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GROWTH

A JOURNAL FOR STUDIES OF DEVELOPMENT AND INCREASE

UNIVERSITY
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VOLUME XVIII, NUMBER 2

PAPERS 451-454

JUNE, 1954 $6.00 A YEAR

Entered as second class matter on October 20, 1941, at the Post Office, Worcester, Mass., under the Act of March 3, 1879.

GROWTH

A journal for the coordination of studies of increase and development as general properties of nature. Published by contributors and subscribers on a cooperative, non-profit, non-salary basis. The field of investigation is primary and work will be published in which the approach is through mathematics, physics, chemistry, genetics, embryology, philosophy, and anthropology; just as will studies of development in its several expressions, and of mass increase and the part played therein by nutrition, vitamins, and hormones.

It is published four times a year during March, June, September and December at $6.00 per volume (outside U. S. and Canada, $6.50). Single numbers $2.00. There will be one volume each year.

All manuscripts and subscriptions should be sent to: The Editors of Growth, Lankenau Hospital Research Institute, Fox Chase, Philadelphia 11, Pa.

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Growth, 1954, **18**, 71-77.

THE PRENATAL GROWTH OF THE THYMUS IN THE DOG

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(Received for publication April 8, 1954)

Although the thymus has been studied for about 300 years, there has been, until recently, much uncertainty regarding its function. Its size and shape have been variously described, both in man and in animals. One who has contributed a great deal to our knowledge of the thymus was Hammar who began to publish on the thymus in 1905 and in 1926 he published a monumental work on the human thymus, in the fetal and postnatal periods, with weights of the entire gland and also a complete analysis of its component parts, including cytological studies.

Hammar ('26) gives a very exhaustive review of the literature and quotes from the various workers, starting with the work of Wharton in 1659; Glisson, in 1671; DeGraaf in 1685 and Blancard in 1687, to all of whom he gives credit for describing the involution of the thymus gland in postnatal life. Further, he says that Blancard recognized a sex and an age difference in its weight, and its postnatal growth was described by Hewson in 1777. According to Hammar, much of this early work is still valid today.

The more recent work on the thymus has been reviewed by Boyd ('32). She has contributed weights of thymus glands from 234 stillborn fetuses and 831 postnatal weights, which she has combined with data from various workers until she has a total of 1891 case records for postnatal growth of the thymus. The prenatal growth of the human thymus is described by Jackson ('09), Scammon ('27), and Ekholm and Niemineva ('50). The growth of the thymus during the fetal period in the cat has been described by Latimer ('39), but so far as is known there are no data on the growth of the dog thymus, either prenatal or postnatal.

MATERIALS AND METHODS

The thymus glands were removed from a series of 187 fetal and 24 newborn dogs and the details of the collection, preservation and

dissection of these will not be repeated for it has been described in earlier publications (Latimer and Corder, '48 and Latimer, '50). Briefly, these fetal dogs ranged from 3.04 to 409.8 gm in body weight and from 55 to 257 mm in nose-anus length. Similar data for the newborn puppies are respectively, 144.5 to 493.5 gm and 164 to 246 mm.

All of the specimens were preserved and stored in a 10% solution of formaldehyde for at least 3 months prior to the dissection, thus insuring adequate preservation and a stabilization of the action of the preservative (Hrdlicka, '06 and Kato, '38). The thymi were removed at the same time that the other organs were removed, and placed in a moist chamber until weighed on an analytical balance to 0.1 mg. The method of plotting these cases, the determination of the empirical formulae and the percentage deviations are all described in the earlier paper (Latimer and Corder, '48). The straight lines in figures 1 and 2 were fitted by the method of least squares and the curvilinear or exponential formula was found by trial and error. The straight lines were phased to fit the individual cases better, without the use of more complex formulae.

Growth in Weight and in Percentage Weight

The growth of the thymus in milligrams during the fetal period is shown plotted on body weight in grams in figure 1, with the dots representing individual fetal males; the circles, individual fetal females; the dots enclosed by circles represent individual newborn males and double circles, newborn females. There is no apparent difference between the weights of the fetal and newborn dogs, so both are included in these formulae. These two straight lines were drawn from the empirical formulae:

$Y = 2.3\ X - 5.62$, from 6 to 62 gm of body weight, and
$Y = 3.4\ X - 73.9$, from 62 to 360 gm of body weight.

Y represents the weights of the thymus in milligrams and X, the body weights in grams. The average percentage deviation of the calculated from the observed values for these curves is 5.73%.

During the first part of the fetal period, the thymus seems to grow more slowly as indicated by the slower rise in the first part of the line. If the line were continued beyond 360 gm of body weight most of the cases in this upper range of weights would be below the line,

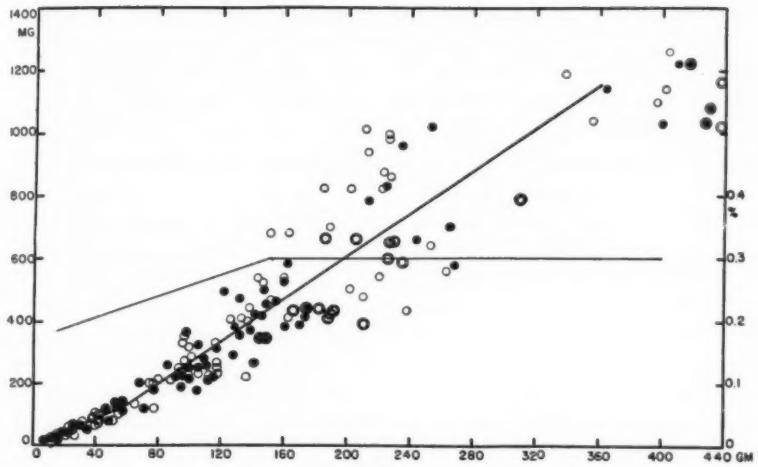

FIGURE 1

The weights of the thymus in milligrams plotted on body weight in grams are represented by the heavier line. The dots represent males; circles, females; dots enclosed by circles, newborn males and the double circles, newborn females. The lighter line with no cases shown represents the percentage weights of the thymus. The empirical formulae used in drawing these lines are given in the text.

or indicating a retardation in the relative growth in these larger fetuses and newborn dogs.

The weights of the thymus as percentages of the body weight are represented by the lighter line in figure 1. The individual percentage weights were plotted on a field graph and they were grouped around the line much as are the weights in this figure. To avoid undue detail in the figure, the individual cases are not shown here. As percentages of the body weight, the thymus increases more rapidly than body weight at first and then above a body weight of 155 gm it forms a horizontal line, or a constant percentage of the body weight. The line representing this percentage weight from 15 to 155 gm of body weight was drawn from the empirical formula:

$$Y = 0.00077X + 0.1816,$$

and above 155 gm of body weight they average 0.297% of the body weight. In this formula, Y represents the percentage weight of the thymus and X, the body weight in grams. The average percentage deviation of the calculated from the observed values is 5.21%.

These same thymus weights plotted on body or nose-anus length are shown in figure 2. With reference to body length the growth of the thymus is more rapid in the later part of the fetal period, as shown by the steeper curve above 148 mm of body length. The empirical formulae from which these two curves were drawn are:

$Y = 0.0013(0.1X)^{4.5} + 0.056X$, from 70 to 148 mm of body length, and

$Y = 9.2X - 1129.9$, from 148 to 250 mm of body length.

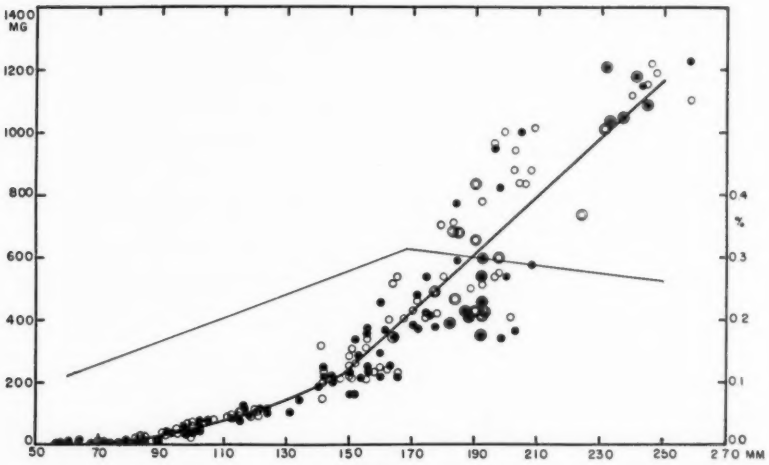

FIGURE 2

The weights of the thymus in milligrams plotted on nose-anus length in millimeters. The symbols are the same as in Figure 1. The lighter lines represent the weights of the thymus as percentages of the body weight. The empirical formulae from which all of these lines were drawn are given in the text.

The symbols are the same as in figure 1 and the average percentage deviation is 4.15%, or slightly less than in the preceding figure.

The weights of the thymus as percentages of the body weight and plotted on body length are represented by the lighter lines without any cases. These lines were drawn from the empirical formulae:

$Y = 0.0019X - 0.003$, from 60 to 168 mm, and

$Y = 0.4216 - 0.00062X$, from 168 to 250 mm.

Y represents the percentage weight and X, the nose-anus length in millimeters. These are not quite so well fitted, for the average percent-

age deviation is 7.34%. Thus we see that the thymus increases to its maximum percentage of the body weight at 168 mm of body length and thereafter decreases slightly.

Discussion

In general, these growth curves for the thymus resemble the similar curves for the fetal growth of the thymus in the cat (Latimer, '39). In both fetal dog and cat, the terminal parts of the curves plotted on body weight are straight lines and the increase in both animals in the latter part of the fetal period, is more rapid with reference to body length. Also the percentage weights, for both animals plotted on body weight, increase more rapidly than body weight at first and then form horizontal lines in the latter part of the fetal period. During the fetal growth of these dogs, the body weight increases 135 times and the thymus 558 times or 4.1 times as much as the increase in body weight. This increase in thymus weight in the fetal dog is a little over half that of the cat whose thymus increases 1061 times or 5.6 times the total increase in body weight for the cat (Latimer, '48). The cat body weight increases more than in the dog or 191 times. Using the figures given by Ekholm and Niemineva ('50), the human thymus increases but 270 times during fetal life and only 2.6 times the increase in total body weight, or body weight and thymic weight increase less in man than in the dog and cat.

The human thymus has been studied extensively and two of the generally admitted facts resulting from these studies are: its variability and secondly, the rapidity with which it responds to deleterious nutritional conditions. In speaking of this variability due to physiological conditions, Simon (1845) says, "It seems to be . . . a barometer of nutrition and a very delicate one." Scammon ('27) gives curves for the prenatal growth of the human thymus. On body weight he shows a single straight line similar to the middle portion of the growth curve in figure 1, and when plotted on crown-heel length the curve is more concave superiorly than in figure 2 for the fetal dogs. Ekholm and Niemineva ('50) illustrate the relative growth of the human thymus gland by a curve increasing throughout the prenatal period. Boyd ('32) has added much to our knowledge of the thymus and in addition has summarized many of the preceding papers on the postnatal growth of the thymus. Freeman ('34) gives additional data on adult thymi from males and females in both whites

and negroes. No review of the literature on the development of the thymus would be complete without listing the work of Hammar ('26). This publication in 1926 is only one of his many studies but it represents the results of years of work. It gives the weights and quantitative microscopic structure for over 1000 human thymus glands in the fetal and postnatal periods.

The structure and growth of the human thymus have been fairly well described. Its variability and susceptibility to modification by changes in the physiological condition have been described by many workers. Its variability is well shown, especially in the later part of the fetal period and in the newborn puppies in figures 1 and 2. In the fetal dog and cat it appears to grow more rapidly than the body weight in the early fetal period and then tends to follow the increase in body weight during the latter part of the period, as shown by the percentage curves in the two figures.

Summary

Throughout most of the fetal period, the thymus of the dog increases as an arithmetical function of the body weight, but at a more rapid rate when plotted on body length.

These weights of the thymus as percentages of the body weight, increase to 155 gm of body weight and thereafter average 0.297% of the body weight. When these same percentages are plotted on body length they reach their maximum at 168 mm of body length and thereafter decrease very slightly.

Empirical formulae are given whereby the weight of the thymus may be estimated from either body weight in grams or body length in millimeters. Formulae are also given for finding the percentages of the thymus from both body weight and body length.

During the fetal growth period of the dog, the body weight increases 135 times and the thymus 558 times or during the fetal period the thymus increases 4.1 times as much as the total body weight. These thymus glands are rather scattered in the figures especially the thymi of the larger fetuses and newborn dogs, indicating some degree of variation.

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Growth, 1954, **18**, 79-96.

ALTERATIONS IN ORGAN AND BODY GROWTH OF RATS FOLLOWING DAILY EXHAUSTIVE EXERCISE, X-IRRADIATION, AND POST-IRRADIATION EXERCISE

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(Received for publication May 18, 1954)

The opinions or assertions contained herein are the private ones of the authors and are not to be construed as reflecting the official views of the Defense Department.

INTRODUCTION

It was previously observed that repeated exhaustive exercise during the post-irradiation period was detrimental to the survival of irradiated rats (Kimeldorf *et al.*, 11; Kimeldorf and Jones, 12; Jones *et al.*, 10). The morphological changes which occur when irradiated animals are secondarily stressed by repeated exhaustive exercise have not been described. The lack of information in the literature concerning the effects of repeated exposure to exhaustive exercise in non-irradiated animals precludes the possibility of extrapolation to the situation of the irradiated animals.

The present study was made to provide information concerning the changes in body and organ weights occurring in rats subjected to (1) daily exhaustive exercise, (2) x-irradiation, and (3) x-irradiation followed by exhaustive exercise. The experimental design made it possible to analyze the sequence of changes following different numbers of exercise trials and different x-ray dosages as well as the changes following various combinations of x-ray doses and post-irradiation exercise trials.

Data will be presented which indicate that x-irradiation and repeated exhaustive exercise affect the weight of several organs in a similar manner, differing principally in the time of maximum effect. The response to combinations of x-irradiation and exercise suggests that repeated exhaustive exercise interferes with the normal pattern of organ weight recovery from irradiation.

METHODS

Eight hundred and sixty-four male Sprague-Dawley rats from inbred colony stock of the U. S. Naval Radiological Defense Laboratory were used in this study. On the first day of exercise, which was also the day of irradiation, all animals were 55 ± 3 days old and weighed 242 ± 14 grams. All animals were caged individually and maintained in temperature controlled rooms. Food (Purina Laboratory Chow) and water were supplied *ad lib*.

In the experimental procedure, exercised and non-exercised animal groups were sacrificed at designated intervals following irradiation and the weights of several organs determined. The experimental design is outlined in Table 1. There were 48 combinations with respect to radiation dose, day of sacrifice and number of exhaustive exercise trials. By allocating two animals for each of the 48 groups in each replication of the experiment it was feasible to test all combinations simultaneously so that the contribution of uncontrollable or unknown factors to the organ response would be shared by all groups. The design was replicated nine times in order to accumulate adequate numbers of animals in each group. However, because of deaths with severe irradiation and exercise, data could not be obtained for all 48 experimental groups. Table 1 also summarizes the number of animals accumulated in each group at the completion of the ninth replication.

TABLE 1

An outline of the experimental design indicating the animal distribution according to experimental conditions, radiation dose, and days of sacrifice. The number of animals accumulated in each group as a result of nine replications of the experiment is noted in parentheses.

X-Ray Dose (r)	Not Exercised Days Post-Irradiation				Exercised Days Post-Irradiation			
	3	9	18	30	3	9	18	30
0	2(18)	2(18)	2(18)	2(18)	2(18)	2(17)	2(17)	2(18)
100	2(18)	2(18)	2(18)	2(18)	2(17)	2(18)	2(18)	2(16)
300	2(18)	2(18)	2(18)	2(17)	2(18)	2(17)	2(14)	2(13)
500	2(18)	2(17)	2(15)	2(12)	2(18)	2(18)	2(11)	2(11)
700	2(18)	2(11)	2(—)	2(—)	2(18)	2(11)	2(—)	2(—)
900	2(18)	2(—)	2(—)	2(—)	2(18)	2(—)	2(—)	2(—)

In the exhaustive swimming test, rats swam individually in 24-gallon cylindrical metal tanks filled with fresh water to a constant level. The water temperature was adjusted to 21°C-25°C. A ten

gram lead weight was clipped to the chest fur of the test animal during each swimming trial. Animals were allowed to swim until they sank and remained below a line approximately eighteen inches beneath the surface of the water for a period estimated to be longer than 30 seconds. The animals were then retrieved and returned to their cages. Most animals could swim 15 to 30 minutes before becoming exhausted under the test conditions. The exercise test was performed daily for five consecutive times per week. With the schedule of swimming tests used, the exercised animals sacrificed on days 3, 9, 18 and 30 were swum to exhaustion for 1, 6, 13 and 21 times respectively.

On the day of sacrifice, animals were weighed and exposed to a lethal dose of ether. The following nine organs were carefully dissected, cleaned and weighed on appropriately sensitive torsion balances; left adrenal, left testis, left kidney, heart, spleen, thymus, pituitary, thyroid and the right gluteus maximus muscle.

The radiation factors were: x-rays, 250 KVP; 15 ma; filters, 0.5 mm. Cu + 1.0 mm Al (HVL, 1.5 mm Cu); target-object distance, 40 inches; dose rate, 25 r per minute measured with Victoreen thimble chambers. Dose measurements in air were accurate within 5% of the dose stated. For exposure to the x-ray beam animals were placed in Lucite chambers spaced radially on a motor-driven turntable which was revolved slowly in the radiation field. The chambers were tilted on the table to approximate an isodose surface. Sixteen animals were placed in the beam at each exposure.

Since all animals were comparable in age and weight at the beginning of the study, comparisons among the various experimental groups were made in terms of the absolute organ and body weights. Pooled estimates of the standard deviation for each organ were calculated and used to assess the significance of differences among various groups sacrificed on the same day. The percentage changes in organ weight from those of normal controls as a result of daily exercise, or irradiation, or irradiation and exercise were also calculated. Where it appears pertinent to the interpretation of data the changes in organ weights with respect to body weight are considered as well.

Results

The mean organ weights for each group are summarized in Table 2. The controls for the study consisted of non-exercised non-irradiated

TABLE 2

Mean body and organ weights for groups of non-exercised (NE) and exercised (E) rats sacrificed at intervals following various doses of x-rays and/or different numbers of exhaustive swimming exercise trials. The difference between two means is statistically significant ($p < .05$) if it exceeds the value listed in column A which is twice its standard error.

Dose (r)	Days of sacrifice 3 NE	3 E	9 NE	9 E	18 NE	18 E	30 NE	30 E	Pooled estimate of standard deviation	Column A
					Body weight (gm)					
0	254	248	269	262	307	280	334	295		
100	244	242	267	259	293	270	326	293		
300	228	233	253	252	291	264	303	264	18	12
500	216	221	231	231	269	221	289	262		
700	215	222	202	195						
900	211	219								
					Gluteus Maximus (mg)					
0	1593	1624	1760	1754	2065	2018	2320	2091		
100	1522	1567	1782	1755	2027	1938	2275	2160		
300	1539	1558	1676	1719	2050	1919	2079	1914	141	94
500	1428	1475	1399	1471	1938	1680	2054	1953		
700	1407	1426	1189	1186						
900	1347	1400								
					Kidney (mg)					
0	1157	1123	1193	1173	1356	1238	1376	1208		
100	1134	1183	1239	1118	1319	1189	1362	1188		
300	1115	1068	1182	1106	1302	1192	1307	1189	99	66
500	1004	1029	1081	1025	1261	1099	1264	1144		
700	976	1008	1058	985						
900	997	908								
					Heart (mg)					
0	841	824	869	882	945	957	970	1018		
100	807	839	873	872	884	934	951	966		
300	786	810	832	833	893	934	902	930	61	40
500	776	782	749	797	888	941	926	892		
700	748	807	717	737						
900	744	787								
					Spleen (mg)					
0	704	672	617	660	624	641	674	686		
100	384	394	468	412	569	555	625	577		
300	286	292	311	305	535	514	585	585	59	39
500	234	254	239	224	468	461	565	566		
700	209	226	193	193						
900	184	204								

TABLE 2 (Continued)

Dose (r)	Days of sacrifice 3 NE	3 E	9 NE	9 E	18 NE	18 E	30 NE	30 E	Pooled estimate of standard deviation	Column A
					Thymus (mg)					
0	528	457	518	439	435	386	401	337		
100	245	224	390	322	394	308	399	309		
300	120	122	158	159	273	237	286	215	51	34
500	99	99	100	84	164	150	187	163		
700	82	80	46	48						
900	72	77								
					Testis (mg)					
0	1395	1410	1528	1507	1567	1527	1630	1658		
100	1392	1445	1493	1367	1366	1404	1275	1220		
300	1378	1381	1362	1344	1324	1328	1006	1004	113	75
500	1371	1350	1290	1231	1175	1186	864	794		
700	1314	1376	1235	1198						
900	1327	1360								
					Pituitary (mg)					
0	10.8	10.5	10.7	10.8	11.2	11.0	11.1	10.9		
100	9.9	10.5	10.7	10.4	10.5	10.2	10.6	10.5		
300	10.1	10.0	10.8	10.3	10.8	10.6	11.4	10.2	1.0	0.7
500	9.7	9.5	10.4	10.1	10.0	9.8	11.2	10.4		
700	9.6	9.5	9.8	9.4						
900	9.6	9.4								
					Thyroid (mg)					
0	16.2	14.9	16.1	16.3	16.7	18.0	16.8	17.2		
100	16.2	15.7	16.3	16.1	17.3	17.3	16.8	17.3		
300	15.9	15.3	16.5	15.6	17.8	18.0	16.9	17.3	1.6	1.1
500	15.3	14.5	14.8	15.9	15.6	17.0	17.7	17.6		
700	14.9	14.5	14.8	13.6						
900	14.1	13.7								
					Adrenal (mg)					
0	23.6	23.6	22.6	27.0	25.0	30.7	24.5	29.4		
100	24.3	25.3	24.7	27.4	25.3	30.5	25.2	30.0		
300	24.4	26.4	24.8	27.9	26.8	31.4	25.4	30.2	2.5	1.7
500	25.5	26.4	25.9	29.7	25.9	29.3	25.7	30.0		
700	27.0	26.9	31.2	29.6						
900	27.8	27.4								

animals and are depicted in the tables and figures as the response of "O" roentgens by non-exercised animals. The effects of exercise in the absence of radiation exposure are represented by the response to "O" roentgens in exercised animals whereas the effects of radiation

in the absence of exercise are represented by the responses to various doses of x-rays by non-exercised animals. The remaining animal group was both exercised and irradiated. Figures 1, 2, and 3 describe the per cent change in mean organ weights of the experimental groups from the controls for each day of sacrifice. The effects of exercise, irradiation, and irradiation followed by daily exercise are considered concurrently for each organ so that the interaction between treatments can be considered.

Body Weight: Daily exhaustive swimming exercise of 15 to 30 minutes duration is capable of significantly depressing the rate of body weight gain from that of the controls (Table 2). The differential in growth between exercised and control animals became larger as the number of swimming trials was increased (Fig. 1). During the 30-day experimental period the body weight gain of swum animals was only 61% of that of control animals. With exposure to x-ray doses of 300 r and greater there was a significant body weight decrease by the 3rd day post-irradiation. The mean body weight of irradiated animal groups continued to be lower than that of control animals sacrificed concurrently throughout the remainder of the study. The initial depression in body weight following x-ray exposure was prolonged in exercised irradiated animals as the number of exercise trials was increased whereas non-exercised irradiated animals tended to approach the body weight of control animals on the later sacrifice dates (Fig. 1).

Gluteus maximus muscle: The gluteus maximus of exercised animals was significantly smaller than that of the controls by the 30th day of the experiment (Table 2). The per cent decrease in body weight with exercise was greater than that of the gluteus maximus for most of the study so that the muscle constituted a proportionately larger part of the body weight in exercised animals than in non-exercised animals despite the reduction in absolute weight of the muscle. Exposure to x-ray doses of 500 r or larger significantly reduced the muscle weight by the 3rd day after irradiation with some recovery observable at later sacrifice periods. This recovery was depressed in irradiated animals subjected to exercise.

Kidney: Exhaustive exercise resulted in a significantly smaller kidney size by day 18 of the study (Table 2). The per cent change in kidney weight with exercise was nearly identical to the per cent change in body weight (Fig. 1) with the result that the proportion of

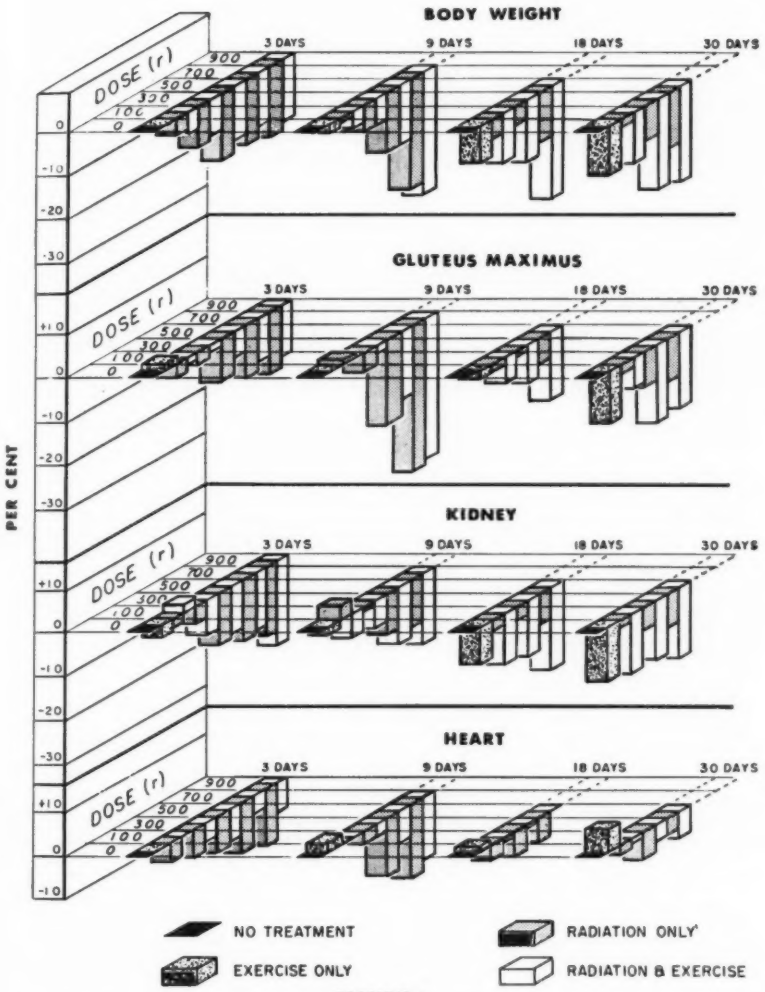

FIGURE 1

The Per Cent change in body and mean organ weights (gluteus maximus, kidney, and heart) of experimental groups from controls according to the x-ray dose and day of sacrifice.

kidney to body weight was undisturbed by exercise in non-irradiated animals. Following exposure to x-rays the pattern of kidney weight changes was similar to that observed in body weight for doses of 500 to 900 r. The per cent decrease in kidney weight was somewhat less than that of body weight on day 9. With the imposition of daily exhaustive exercise on irradiated animals there was no recovery from the initial depression in weight induced by irradiation (Fig. 1).

Heart: The heart of animals subjected to daily exhaustive exercise was significantly larger than that of controls by the 30th day of the experiment (Table 2). Because of the concurrent reduction in body weight with this type of exercise the heart constituted a much greater portion of the body weight in exercised animals than in controls for most of the study. Exposure to x-ray doses of 300 r and greater resulted in a significant reduction in heart weight. The response was most pronounced on day 9 with exposure to lethal doses of x-ray. The per cent decrease in the heart weight of irradiated animals was less if these animals were exercised after irradiation (Fig. 1). Although the degree of relative cardiac hypertrophy induced by exercise in irradiated animals rarely achieved the 5% level of significance in comparison between individual groups, it was evident in the majority of cases when irradiated groups were exercised.

Spleen: The spleen of exercised, non-irradiated animals was significantly larger than that of controls on the 9th day of the study (Table 2). Exposure to all doses of x-rays markedly reduced the spleen size on all days of sacrifice. The response was maximum on day 3 at which time the spleen was 45 to 75% smaller than the control, depending upon the x-ray dose (Fig. 2). A trend toward recovery in weight was evident at later times of sacrifice. The response of the spleen to irradiation did not appear to be altered appreciably by post-irradiation exercise.

Thymus: The thymus weights were reduced after a single exercise trial and remained smaller than those of the controls for the duration of the experiment (Table 2). The magnitude of this depression appeared to be independent of the number of exercise trials. The thymus showed the greatest response to irradiation of all the organs studied, with reductions of 58-85% from the control groups occurring on day 3 post-irradiation. There was a much smaller difference between controls and irradiated animals by the 18th day post-irradi-

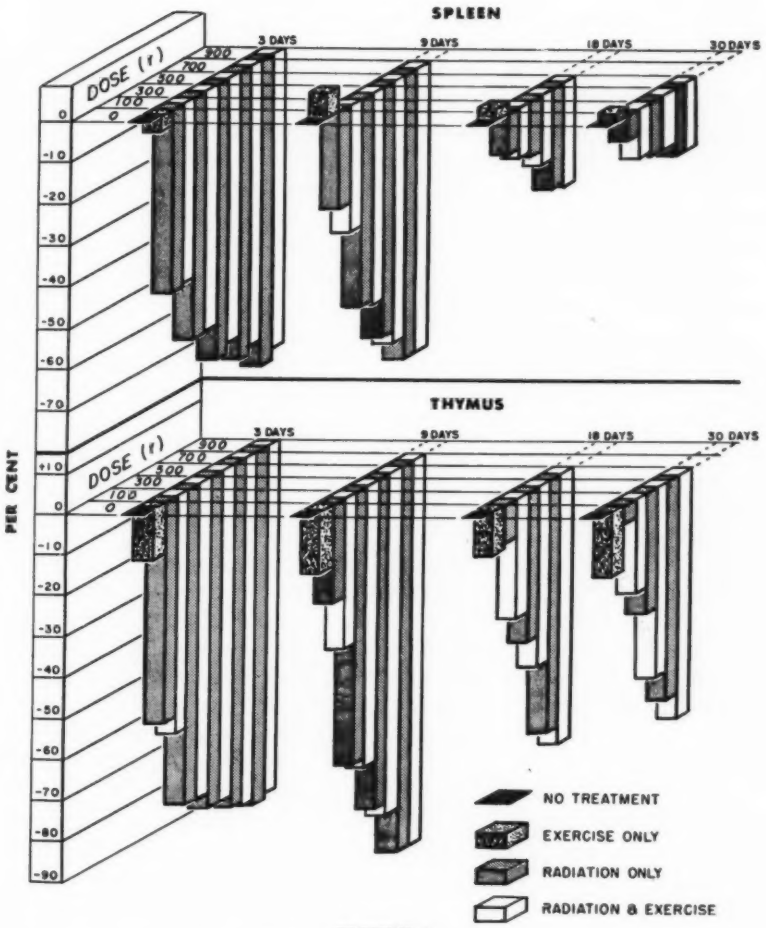

FIGURE 2

The Per Cent change in mean organ weights (spleen and thymus) of experimental groups from controls according to the x-ray dose and day of sacrifice.

ation (Fig. 2). A portion of this apparent recovery may be attributed to an 18% decrease in thymus weight of the controls for the same period (Table 2). Post-irradiation exercise was effective in reducing significantly the thymus size of rats exposed to 100 r by day 9 and to 300 r by day 18 (Fig. 2).

Testis: The absolute weight of the testis was not appreciably altered by the number of exercise trials used in this study (Table 2). Testicular weight was maintained despite the decrease in body weight with exercise. Following exposure to x-rays the testis exhibited a decreasing weight with time after irradiation. The maximum effect was observed on the 30th day after irradiation (Fig. 3). Post-irradiation exercise had very little effect upon the response of the testis to irradiation.

Pituitary: Daily exhaustive swimming had no effect on pituitary weight of non-irradiated animals. There was a significant decrease in pituitary weight on the 3rd day following irradiation and the gland tended to be smaller than that of the non-irradiated controls through day 18 of the post-irradiation period (Fig. 3). When irradiated animals were exercised the only significant shift in pituitary size was a decrease in weight following 300 and 500 r on day 30 post-irradiation (Table 2).

Thyroid: A decrease in the thyroid weight of non-irradiated animals following exercise was observed on the 3rd day of the study (Fig. 3). The trend was subsequently reversed so that, by the 18th day, the thyroid gland of exercised animals was significantly larger than that of control animals. The thyroid response to irradiation was variable, and a consistent trend was difficult to ascertain. In most cases the thyroid weight was reduced following lethal doses of radiation (500 to 900 r) on the 3rd and 9th day after irradiation. By day 30 the thyroids of irradiated animals were similar to, or slightly larger than, their controls. The thyroids of exercised irradiated animals were significantly larger than those of non-exercised irradiated animals on days 9 and 18 after 500 r and smaller on day 9 after 700 r.

Adrenal: The adrenal size was unaffected by exercise on the 3rd day of the study which was 48 hours after the initial swimming trial. However, for the remainder of the study the adrenals of exercised animals averaged 21% larger than the control glands (Fig. 3). This response to daily exhaustive exercise was the most marked of all

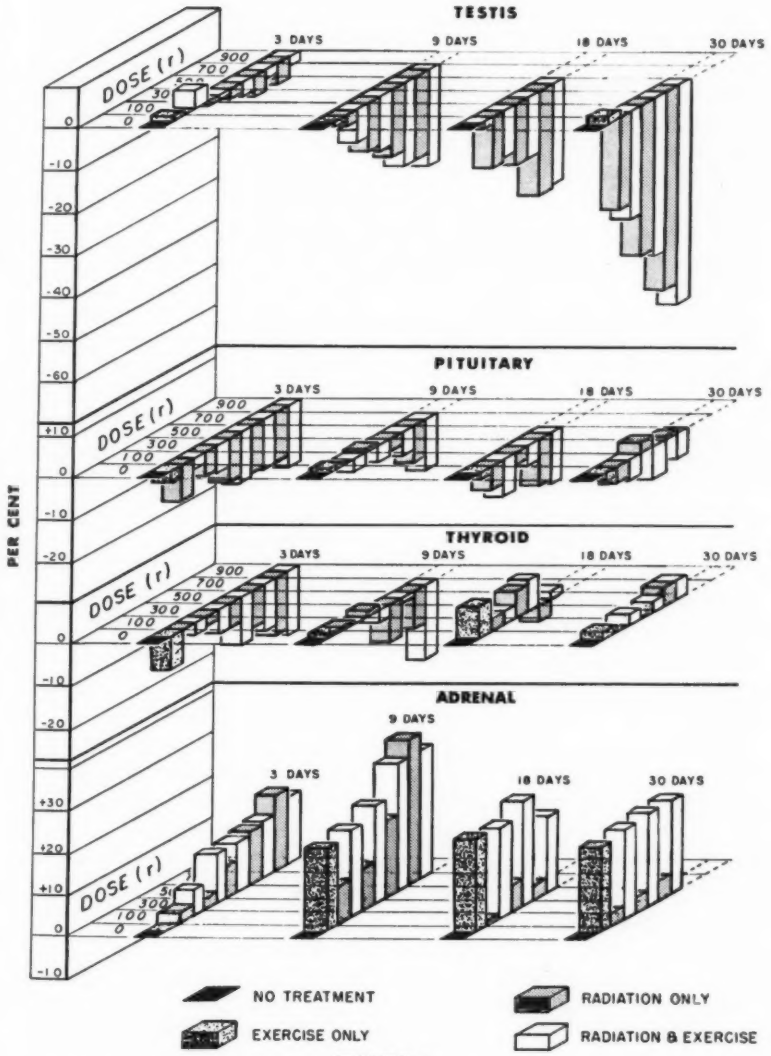

FIGURE 3

The Per Cent change in mean organ weights (testis, pituitary, thyroid, and adrenal) of experimental groups from controls according to the x-ray dose and day of sacrifice.

organs studied. The non-exercised irradiated groups showed adrenal enlargement after lethal doses on day 3 and for all doses on day 9 post-irradiation (Table 2). The regression in adrenal weight which occurs typically in irradiated animals by the 18th day is prevented by post-irradiation exercise and the adrenals remained enlarged during the course of observation (Fig. 3).

Discussion

The Effects of Repeated Exhaustive Swimming Exercise

The reduction in body growth with repeated exhaustive swimming exercise is probably the result of an increased energy expenditure through exercise accompanied by a concurrent decrease in food consumption. Food consumption has been found to decrease during periods of swimming exercise in rats (Whalley *et al.* 23) and with forced exercise in a motor driven treadmill (Selye, 15). Whalley *et al.*, (23) concluded that this decrease is reflective of a depressed desire to eat under conditions of physical stress. The gluteus maximus muscle weight changes with exhaustive exercise in the present study are similar to those observed by Steinhaus *et al.* (20) using dogs which were swum to exhaustion. The absolute weight of the leg musculature was reduced but, relative to body weight, the musculature was larger in the exercised animals. Steinhaus *et al.* (19) also observed an increase heart volume in dogs after three weeks of swimming exercise which is similar to the time required for a significant increase in heart weight of rats in the present study.

The responses of the kidney, testes, thyroid, spleen and body weight of rats which have been exercised repeatedly by swimming to exhaustion differ in some respects from those reported for volitional exercise (Hatai, 9; Donaldson, 5) and for forced exercise in motor-driven wheel cages (Selye, 15; Anderson, 1; Constantinides, 3). Most of these apparent discrepancies can probably be resolved on the basis of differences in the factors of work intensity, duration of exercise, and the degree of repetition of the exercise experience imposed. The marked adrenal enlargement, thymic involution, and reduction in body growth have been observed to varying degrees in other studies of exercise performance in rats (Selye, 15; Anderson, 1; Guerrant, *et al.*, 8).

Some degree of physical activity is generally considered desirable

for the well-being of most animal species. Repetition of physical effort in the form of exercise results in functional and structural adaptations which facilitate the performance of more exercise. The total sum of these adaptations constitutes the "trained state" (Steinhaus, 21) attained through a period of repeated exercise. The general adjustments associated with the trained state have been reviewed by Steinhaus (21). If, however, animals are forced to participate in an exercise much longer than they would voluntarily, or to the point of exhaustion, then signs of stress become apparent. Some of the more common morphological changes which occur as a result of exposure to stressful situations are adrenocortical enlargement, thymolymphatic involution, gastric ulcers, and reduced body weight (Selye, 15). These responses can be considered as non-specific since they occur regardless of the nature of the stressing agent. Most experiments utilizing a method of enforced exercise result in changes which are the combined effects of the non-specific responses to the stress of forced activity and the responses specifically related to the adaptations to exercise. Accommodations to the conditions of exercise are evident in the present study by cardiac hypertrophy and, possibly, by a relative although not an absolute, increase in the size of muscle (gluteus maximum) participating in the exercise. The more marked changes in the remaining organs are predominantly those which occur during conditions of chronic stress.

Effects of Total Body X-Irradiation: Data on weight changes in particular organs following x-irradiation have appeared in the literature (Carter, *et al.*, 2; Patt, *et al.*, 14; Eschenbrenner and Miller, 7). In contrast to previous observations the present study described the concomitant effects in several organs with respect to dose dependency as well as the rate of recovery. The effects of radiation upon organ weight, with the exception of the testis, appears to be prompt so that the maximum effect is attained in animals sacrificed on the 3rd or 9th post-irradiation day. In general, these changes tend to subside so that most organs approach normal organ weight levels during a 30-day post-irradiation period.

The testicular atrophy is such that the maximum decrease occurs at 30 days post-irradiation. This pattern of testicular change has been shown to be the consequence of the inhibiting effects of radiation upon mitotic activity during the process of spermatogenesis in the mouse. (Eschenbrenner and Miller, 7). Since inhibition of mito-

sis results in fewer dividing spermatogonial cells the reduction in organ weight at four weeks presumably reflects the decrease in numbers of maturing spermatogenic elements.

The relationships between x-ray dose and body weight in the rat have been analyzed in detail by Nims and Sutton (13). The data in the present study tend to confirm their finding that the time for recovery of body weight is a function of the x-ray dose. The weight response of the gluteus maximus, heart and kidney appear to follow closely that of the body weight. The parallel pattern of changes in these organs suggests that a similar mechanism may be operative, perhaps as a result of post-irradiation anorexia. The response of the gluteus maximus muscle and the kidney does not appear to be as sensitive as the body weight since significant changes occur with 300 r in body weight and 500 r in the organs.

Of all organs tested the spleen and thymus showed the greatest response to radiation. The per cent reduction in spleen weight on day 3 following irradiation was a linear function of the logarithm of the x-ray dose. A similar dose-response relationship was also observed in the thymus on day 3 after x-ray doses of 300 r or larger (Fig. 4). This dose-response proportionality of spleen and thymus was demonstrated by Carter, *et al.* (2) for the mouse for day 5 post-irradiation. It is apparent that a similar proportionality exists for these organs in the rat. The dose response of the testis on day 30 was also found to fit the same general formula; however, the response could be determined only for x-ray doses of 100, 300 and 500 r since survivors were not available for testing at higher doses (Fig. 4).

From the evidence available adrenal participation in the radiation syndrome does not appear to be different from that occurring with other stresses. The changes in adrenal weight, cholesterol, and ascorbic acid content (Patt, *et al.*, 14; Wexler, *et al.*, 22) as well as the responses to cortical functional tests (Smith, 18) in irradiated rats and mice are those known to occur following a variety of noxious stimuli. Adrenalectomy increases radiation mortality (Cronkite and Chapman, 4) while corticoid therapy is beneficial in irradiated adrenalectomized animals (Edelmann, 6) but not in animals with intact adrenals (Smith, *et al.*, 17).

Effects of Post-Irradiation Exhaustive Exercise: The imposition of daily exhaustive swimming exercise after irradiation results in a sequence of responses reflecting the earlier changes which accompany

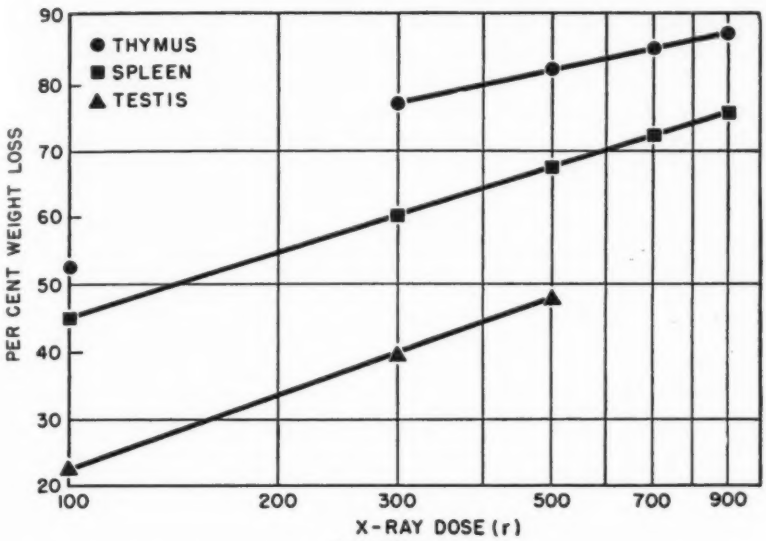

FIGURE 4

Per Cent reduction in organ weight as a function of x-ray dose plotted on semilog scale. The spleen and thymus weights were obtained from animals sacrificed on the third day post-irradiation while the testis weights were from animals sacrificed on the thirtieth day post-irradiation.

radiation in combination with cumulative changes which occur with successively greater amounts of exercise. It was not anticipated that exercise would alter markedly the response to x-rays on the third day post-irradiation since only one exercise trial occurred by this time. The effects of a single exercise trial are probably masked by the much greater effects of radiation at this time. The response to exhaustive exercise in the irradiated animals is largely a repression of recovery from irradiation rather than an accentuation of radiation effects. This is most clearly demonstrated by the changes in body weight, gluteus maximus, kidney, thymus (at sublethal doses) and adrenal weight. The organ size in exercised irradiated animals is the result of interaction between the effects of exercise and irradiation and does not appear to be a simple sum of their separate effects. The degree of synergism is related to the size of the radiation dose and the number of exercise trials prior to sacrifice with the most pronounced effects appearing in exercised irradiated animals sacrificed after potentially

lethal doses of radiation. The adrenal gland is especially sensitive to the interaction of radiation and exercise. Significant changes in adrenal weight were not observed following sublethal doses of x-rays nor did exercise produce a significant change by day 3 of the experiment. However, when animals were exposed to sublethal x-ray doses and exercised for a single trial there occurred a significant increase in adrenal size.

The specific effects of exercise upon heart weight and irradiation upon testicular weight are both apparent in the exercised irradiated animal. The changes in body weight, kidney, adrenal, thymus, pituitary and possibly thyroid appear to be largely non-specific responses since they occur to a degree with either exercise or total body irradiation.

Both radiation and exhaustive exercise have been described as being particularly effective in eliciting symptoms of the general adaptation syndrome of Selye (16). It appears that the imposition of repeated exhaustive exercise upon an animal previously stressed by irradiation deters recovery in terms of organ weight. These results suggest that the increased mortality with repeated exhaustive exercise after irradiation may be explicable in terms of the inability of the irradiated animal to cope with the additional stress of exhaustive exercise.

Summary

Male rats were subjected to the stress of repeated exhaustive swimming exercise or to several doses of x-rays or to various numbers of exhaustive swimming trials after irradiation. A quantitative analysis was made of the body weight and the weights of nine organs at various intervals after imposition of the experimental condition. The body weight, gluteus maximus, kidney and thymus weights were reduced while the adrenal weight was increased in animals subjected to daily exhaustive exercise or exposed to x-rays. The spleen and heart were enlarged on particular days of sacrifice following exercise; whereas they were reduced with most doses of x-rays. The testis and pituitary weights were decreased by irradiation but not by exhaustive exercise. In general, changes following irradiation are related to the x-ray dose and are prompt, while the changes with repeated exhaustive exercise are accumulative and dependent upon the number of exercise trials. When irradiated animals are exercised to exhaustion the initial organ weight responses are predominantly those following ir-

radiation and they are not markedly increased by exercise. However, repeated exhaustive exercise tends to sustain the earlier radiation changes and interfere with the normal pattern of organ weight recovery from irradiation.

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COMPARISON OF LEWIS RAT LYMPHOMA WITH OTHER BLOOD-BORNE NEOPLASMS[1]

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(Received for publication June 1, 1954)

When it was found, that the lymphoma #8 which arose spontaneously in the throat of a rat of the Lewis inbred strain could be transmitted into normal rats by injections of blood from rats bearing the lymphoma (23), it seemed of interest to compare the behavior of this lymphoma with that of other blood-borne neoplasms such as chicken leukosis (10, 11, 33), mammalian lymphosarcoma (12, 32) and myxoma (20, 38). The study was approached from four different angles:

I. Appearance of the neoplastic cells in the blood stream of lymphoma implanted rats.

II. Amount of blood required to bring about the growth of a lymphoma when injected into susceptible animals.

III. Survival of the lymphoma #8 following exposure to low temperatures.

IV. The fraction of the blood (buffy coat, plasma or serum) containing the lymphomatous material.

MATERIAL AND METHOD

Rats of the Lewis inbred strain were used in these studies. Rather large rats, 60 to 70 days old, were used for implantation of tumor tissue and for collection of blood. Blood was drawn by means of a 10 ml syringe with a #22 needle, from the heart of a rat, which had been implanted with lymphoma, and injected into the subcutaneous tissue on the right side of normal young rats 40 to 50 days old. In most instances, the amount of whole blood, suspensions of buffy coat, plasma or serum injected into normal rats was equivalent to 1 to 2 ml; in a few experiments, as much as 5 to 7 ml of whole blood was used. All implantations of tissue or injections of blood to be tested were made into the subcutaneous tissue of the right side. The tumor

[1] Aided in part by a Grant from the National Cancer Institute of the National Institutes of Health, Public Health Service, Bethesda, Md.

tissue was implanted by means of a trochar consisting of a #13, 3½ in. stainless steel hypodermic needle with a close-fitting plunger. The amount of tissue implanted was equivalent to ½ a trochar-full.

Treated rats were kept under observation for 21 to 35 days. Then the tumor resistance of those in which tumor failed to develop was challenged by an implantation of a tiny graft of lymphoma tissue, or by an injection of ¼ ml of whole blood from a lymphomatous rat. All challenges were introduced into the left side of the treated rats.

I. *Appearance of the neoplastic cells in the blood of rats implanted with lymphoma*

Blood was drawn from the heart, at various intervals, after implantation of lymphoma tissue, and injected into normal young rats. The majority of rats used in this study received 2 ml of whole blood drawn 18 hours, 22 hours, 1, 2, 3, 4, 6, 8 and 10 days after implantation of lymphoma tissue.

Results

Table 1

The results given in Table 1 show that the lymphoma-producing cells were present in the blood of 66 per cent of the rats as early as 18 hours after subcutaneous implantation of lymphoma tissue, and in 83 per cent of the rats injected with blood drawn three and four days after implantation of lymphoma tissue. Every one (100%) of the rats injected with blood drawn six or more days after implantation of lymphoma tissue developed a lymphoma at the site of injection.

Transmission of lymphoma #8 by means of blood has been carried through 12 successive passages in rats of the Lewis inbred strain. The

TABLE 1
APPEARANCE OF NEOPLASTIC CELLS IN BLOOD OF RATS

Time blood was drawn after subcut. implant. of lymphoma in rats	No. rats injected	Number tumors	Per cent tumors
18 hours	6	4	66
22 "	6	4	66
24 "	6	4	66
48 "	6	4	66
3 days	6	5	83
4 "	6	5	83
6 "	6	6	100
8 "	6	6	100
10 "	6	6	100

lymphomata that originated from injections of whole blood resembled those resulting from implantation of lymphoma tissue both morphologically and histologically.

It seemed of interest to test whether neoplastic cells might be present in the blood stream of animals bearing other types of neoplasms. For this purpose, a number of rats of the Lewis inbred strain were injected with as much as 6 to 7 ml of blood drawn from the heart of a rat bearing one of the 100 per cent transplantable methylcholanthrene-induced sarcoma (#2, #9, #10, #12) or fibrosarcoma (#3, #4, #7). The experiment was repeated six times. Tumors failed to develop in all of the 42 rats injected. Whole blood or suspensions of washed buffy coat from rats of the P.A. (Aptekman) inbred strain bearing sarcoma #6 were injected into rats of the same strain. Tumors failed to grow in any of the rats injected.

Twelve rats of the Lewis inbred strain were injected with 6 to 7 ml of blood from rats of the P.A. strain bearing sarcoma #6. Tumors failed to develop in every one of the twelve rats injected with blood from alien strain tumor-bearing rats.

On the other hand, tumor-producing cells were found in the blood of mice of the Lewis inbred C57 strain bearing the transplantable bladder carcinoma #150 which occurred spontaneously in the bladder, or the lung carcinoma #16 which originated in the lungs. Each of these neoplasms metastasized to the lungs of the host. Injections into normal young C57 mice of ¾ ml of whole blood drawn from a carcinoma-bearing mouse resulted in a rapid growth of a carcinoma in 100 per cent of the 46 mice injected with blood from mice bearing lung tumor #16 and in 80 per cent of the 43 mice that received blood from mice with bladder carcinoma #150.

The resistance of rats in which tumors failed to develop was challenged by implantations of tissue from a sarcoma or fibrosarcoma native in its strain. For instance, rats of the inbred P.A. or Lewis strain in which blood from rats of that strain failed to grow, were challenged by implantations of a tumor native in their own strain. Rats of Lewis strain which received blood from the alien strain, namely, P.A. rats bearing sarcoma #6, were challenged by implantation of Lewis fibrosarcoma #4. The challenge grafts grew in every one of the negative rats indicating that injections of whole blood, even blood from an alien strain of rats, failed to protect the treated animals from the growth of a subsequent implantation of tumor tissue that originated in its own strain.

Discussion

The presence of a tumor-producing agent other than living neoplastic cells was first demonstrated in relation to spontaneous chicken sarcoma and spontaneous fowl leukosis (10, 11, 15, 25, 37). Lewis and Andervont (25) found that chicken sarcoma could be transmitted by either plasma or cells from blood of sarcomatous chickens; *in vitro* studies indicated that the neoplastic cell corresponded to hypertrophied monocytes (24). A number of investigators noted that lymphoid and myeloid leukemia of mice could be transmitted to normal mice by injection of whole blood, malignant lymphoid cells, and malignant myeloid cells from leukemic mice but not by plasma or cell-free filtrates (1, 12, 16, 17, 18, 36). In studies of leukemia, lymphosarcoma and lymphoma of rats, it was found possible to transplant the disease to normal rats by injections of whole blood or of white blood cells from diseased rats (32, 23). Several observers (10, 22, 38, 40) studying the infectious myxoma of rabbits, noted that the tumor could be transmitted to normal rabbits of a given strain by injections of cell-free as well as cellular portions of blood or of tumor extracts.

The majority of observers tested the tumor-producing property of the blood of animals bearing large tumors or having pronounced leukemia; few studied the time after inoculation when the neoplastic agent appeared in the blood stream of treated animals. Burmester and Cottral (4) noted that whole blood of fowl 7-day intramuscular transplants of lymphoid tumors produced visceral tumors and death of all fowl inoculated. Burmester, Prickett and Belding (5) found that filtered[2] plasma from blood drawn from a chicken 8 days after it was inoculated with lymphoid tumor tissue transmitted the disease to normal chickens. Sanarelli (38) and later Hobbs (20) noted that blood of rabbits inoculated with myxoma was infectious to normal rabbits within 48 hours after inoculation of the host. In the present study, the neoplastic cells were found in the blood stream as early as 18 hours after subcutaneous implantation of lymphoma tissue.

Serial transmission of chicken sarcoma was carried through 4 successive passages by means of whole blood cells or of plasma (25) and through six serial passages by injections of filtered plasma (4). In the present study transmission of lymphoma #8 by means of blood

[2] Berkefeld, Seitz and Selas filters were used by various investigators.

was carried through 12 serial passages in rats of the Lewis inbred strain.

II. *The amount of whole blood required to produce lymphoma when injected into susceptible rats*

Growth of lymphoma following injections of whole blood from lymphoma-bearing rats did not seem to be dependent upon the amount of blood injected. In the present study it was found that as little as ½ minim of whole blood or 1 ml of a suspension (1 drop of blood diluted with 200 parts of Locke's solution) gave rise to a lymphoma in about the same length of time as injections of 1 or more milliliters of whole blood. Injections of plasma or serum that had been centrifuged only once, and, therefore, most likely containing one or more blood cells, transmitted the disease to about 75 per cent of the rats injected. In many instances the time required for development of lymphoma following injections of greatly diluted blood was considerably longer than that needed for growth of implants of lymphoma tissue.

Discussion

The amount of tumor-producing material injected into normal animals does not seem to influence the development of the disease in the treated animals. Myeloid cells from mice with myeloid leukemia, in dilutions of 1 to 400, transmitted the disease (12). Inoculations of as few as 10, in some instances only one, malignant lymphocytes produced leukemia in mice (14). As small an amount as 0.00001 ml of blood from chickens with leukosis or sarcoma produced tumors when injected into normal chickens (41); 1 drop of blood from a rabbit with myxoma, diluted in 200 ml of broth, was found to be infectious (8). Claude (6) found that the dry weight of the leukosis-producing particles sedimented from ultrafiltrates[2] of chicken tumor agent was 0.0008 mg per ml of filtrate. Purified filtrates of chicken tumor containing as little as 5 mg of nitrogen per 100 ml of filtrate, transmitted the disease (31). Tumor-producing extracts of avian leukosis purified by adsorption with aluminum hydroxide (3), which removed practically all of the proteins as was demonstrated by chemical tests as well as sensitization tests in guinea pigs and complement fixation tests in rabbits. The latter indicated a concentration of protein less than one part in 1,000,000,000 in purified extracts which exhibited a

tumor-producing activity even more pronounced than the original extract. Preparations of chicken lymphomatosis purified by three successive centrifugalizations at 15,000 r.p.m. were infectious in amounts containing 3.2×10^{-7} or 8.6×10^{-8} mg. of nitrogen (19).

Lewis and Mendelsohn (26) noted that Berkefeld filtrates of the chicken tumor agent from which protein had been removed by adsorption with kaolin or charcoal remained infectious even though all protein demonstrable by the Biuret or nitric acid ring tests had been removed. Ultrafiltration studies of the active agent of chicken tumor (27) indicated that the agent passed through 3%, 4% and in some instances 5% collodion membranes, thus indicating that its size was less than 40 millimicrons. The extracts that passed the collodion membranes were infectious although free from all protein demonstrable by the Biuret, ninhydrin and nitric acid ring tests. Also, it was found (22) that the supernatant fluid of centrifugalized extracts of rabbit myxoma that had been cleared of protein by adsorption with aluminum hydroxide remained potent. Nitrogen determinations of the purified extracts of rabbit myxoma varied in the region of 0.5 mg. per 100 ml of filtrate.

III. *Survival of lymphoma #8 following exposure to low temperatures*

In earlier studies, it was noted that storage in the refrigerator for one to three days did not interfere with later growth of lymphoma #8 when implanted in susceptible animals. It seemed of moment, therefore, to determine how long lymphoma tissue and blood from lymphomatous rats remained viable when kept in the refrigerator at 4°C., and in the freezer at —7°C. For this purpose, rats of the Lewis inbred strain with lymphoma #8 were bled from the heart and 1¼ ml of the blood placed in each of three sterile vials. Following this the lymphoma was removed and sufficient tissue to implant one rat was placed in each of three sterile vials. The six vials, 3 containing blood and 3 containing lymphoma tissue, were deposited in the freezer at —17°C. A duplicate set of 6 vials was placed in the refrigerator at 4°C. After varying intervals of time the vials were removed from the cold and the material implanted into susceptible young rats. The experiment was repeated five times giving a total of 105 rats implanted with lymphoma stored in the refrigerator, and 105 rats implanted with tissue stored in the freezer.

The blood became clotted during storage, and it was necessary to mince the clot to release the cells. More than one vial had to be used to furnish the 1 ml required for each injection. For this reason only six rats were injected with blood kept in the refrigerator, and six with blood kept in the freezer. The experiment was repeated three times, giving a total of 18 rats implanted with lymphoma from the refrigerator and 18 rats were implanted with lymphoma from the freezer.

Fifteen normal rats were implanted with lymphoma tissue and 15 with blood that had been stored for one hour at room temperature to serve as controls of the tumor-producing activity of blood and of tumor tissue exposed to temperatures of 4°C. and —17°C.

Results

Table 2

The results given in Table 2 indicate that both lymphoma tissue and blood from lymphomatous rats remained viable when stored in the refrigerator for five days. The lymphoma tissue remained viable

TABLE 2

Exposure of Lymphoma #8 to Low Temperatures

Lymphoma in Refrigerator			Lymphoma in Freezer		
No. rats injected	Days in refrig.	Number tumors	No. rats injected	Days in freezer	Number tumors
15	3	15	15	3	15
15	5	15	15	5	15
15	6	2	15	6	15
15	9	0	15	9	15
15	12	0	15	12	15
15	18	0	15	18	15
15	24	0	15	24	15
Blood in Refrigerator			**Blood in Freezer**		
No. rats injected	Days in refrig.	Number tumors	No. rats injected	Days in freezer	Number tumors
6	5	5	6	5	6
6	6	2	6	6	4
6	12	0	6	12	0
Controls					
Lymphoma at Room Temperature			Blood at Room Temperature		
No. rats injected	Days in refrig.	Number tumors	No. rats injected	Days in freezer	Number tumors
15	0	15	15	0	15

when stored in the freezer for as long as 24 days.[3] On the other hand, blood from the lymphomatous rats stored either in the refrigerator or in the freezer for 12 days failed to transmit the disease. Tumors grew in all of the controls, namely, the 15 rats implanted with lymphoma tissue and the 15 rats injected with blood that had been kept at room temperature for one hour.

The tumor resistance of rats in which tumors failed to grow was challenged. Every one of the challenged rats developed a lymphoma on the left side, showing that the previous treatment with tumor tissue or blood stored in the refrigerator or freezer had not brought about the development of tumor resistance in the treated rats.

Discussion

A number of investigators noted that leukoses and sarcomata from fowl and from mammals remain viable when stored at subzero temperatures for various lengths of time. The early publications seem to indicate that blood of leukemic animals is more susceptible to cold than tumor tissue from the same animal. This, however, is difficult to ascertain as the distinction between leukemic blood and cells present in leukemic animals is not always clearly stated. The results given by some investigators (11, 12, 13, 17) indicate that the thermal death point of cells from fowls and from mice with leukosis was between —10°C. and —20°C. Other investigators (1, 11) point out that filtered plasma and tumor extracts as well as cells of fowl sarcomata and fowl leukoses remain infectious when kept frozen at —60°C. to —76°C. Furth (11) claimed that mouse leukemic lymphocytes were destroyed by freezing at —10°C. to —20°C., but that blood cells of avian lymphomatosis survive freezing at —70°C. for 30 minutes. Burmester (3) found that leukemic lymphocytes from spontaneous avian lymphomatosis remained viable at temperatures between —65°C. and —76°C.; one sample tested after storage for 5.5 years was found viable. Cells of mouse leukemia could be preserved if stored at temperatures of —70°C. Warner and Gostling (42) found that mouse sarcoma 37 retained its transplantability after exposure to temperature of —79°C. for 182 days. Murphy and Sturm (32) found that rat lymphoma frozen[4] for 14 days was still transplantable, but frozen blood failed to transmit the disease. Splendore

[3] Probably many more days.
[4] Temperatures not stated.

(41) noted that infectious myxoma of the rabbit retained its viability for many days in the refrigerator. Klinke (21) found that various types of neoplasms remained transplantable after freezing for various lengths of time in liquid nitrogen at nearly —196°C.

The present study indicates that there is a marked difference in degree of cold and time of exposure at which blood and tumor tissue from lymphomatous rats can remain viable. Lymphoma tissue remained transplantable during storage for 24 or more days in the freezer at —17°C., but whole blood from the same rats became inactivated when stored for longer than 6 days in either the refrigerator or the freezer.

IV. *The fraction of the blood (buffy coat, plasma and serum) containing the lymphoma-producing material*

When it was found that injections of minute amounts of blood from lymphomatous rats transmitted the disease to normal rats, it seemed of interest to determine in which portion of the blood (buffy coat, plasma and serum) the neoplastic agent was located. For this purpose 6 to 10 ml of heparinized blood[5] drawn from a rat bearing a moderately large lymphoma were centrifugalized for 15 to 20 minutes at 2500 r.p.m. The supernatant plasma was then pipetted off into clean sterile tubes and the buffy coat lifted off into 20 ml of sterile Locke's solution and cut into several large fragments. The pieces were washed through several changes of Locke's solution and then removed to 5 ml of Locke's solution, and minced into an even suspension of cells to be used for injection. The saline washings were collected from the various dishes and centrifugalized. When serum was to be used the blood was drawn without heparine and placed in the refrigerator until it became clotted. The clot was loosened and the tubes of blood centrifugalized for 20 minutes at 2,000 r.p.m. The serum was then pipetted off into a clean tube. The amounts used for injection into normal rats were: 1 ml of the suspension of buffy coat cells: 2 to 3 ml of the saline washings of the buffy coat; and 2 to 3 ml of plasma or serum.

[5] Sodium oxalate plasma was toxic.

Results

Table 3

The results given in Table 3 show that every one of the 100 rats injected with whole blood and every one of the 50 rats injected with suspensions of the buffy coat developed a lymphoma. Twenty-five of the 35 rats (71.2%) injected with plasma, 30 of the 70 rats (42.8%) injected with serum, and 30 of the 70 rats (42.8%) injected with

TABLE 3
FRACTION OF THE BLOOD CONTAINING THE LYMPHOMATOUS MATERIAL

Material used	No. rats injected	Number tumors	Per cent of rats +
Whole blood	100	100	100
Buffy coat	50	50	100
Plasma	35	25	71.2
Serum	70	55	78
Saline washings	70	30	42.8
	Recentrifugalized		
Plasma	30	4	13.3
Serum	62	12	19.3
Saline washings	25	0	0
	Twice Recentrifugalized		
Plasma	50	0	0
Serum	55	0	0
Saline washings	30	0	0

saline washings of the buffy coat developed lymphomata at the site of injection. From these results it seemed obvious that the centrifugalization had been incomplete. In some instances, microscopical examination of material from the bottom of the tubes revealed the presence of a few cells. The supernatants were therefore pipetted off into clean tubes and recentrifugalized. Injections of the recentrifugalized material resulted in growth of lymphomata in 4 of the 30 rats(13.3%) injected with plasma, and in 12 of the 62 rats (19.3%) injected with serum. The 25 rats injected with saline washings failed to develop lymphomata. The centrifugalized supernatants were pipetted into clean tubes and again centrifugalized. The 50 rats which received the twice-centrifugalized plasma, the 55 rats injected with the twice-centrifugalized serum, and the 30 rats injected with the twice-centrifugalized saline washings failed to develop lymphomata. These results indicated that it is possible to obtain plasma

or serum free from the lymphoma-producing agent, provided the material is centrifugalized more than once. From this it was concluded that the cellular and not the cell-free fraction of the blood of lymphomatus rats transmitted the disease.

Microscopical examination of stained preparations of the buffy coat showed that it was composed almost entirely of lymphoid cells resembling those present in sections of the lymphoma (23).

Rats free from tumor implanted with a challenge graft of lymphoma tissue or injected with ¼ ml of whole blood from a lymphomatous rat, developed lymphoma, showing that treated rats used in the experiment had not developed resistance to growth of lymphoma cells.

Discussion

Many investigators have attempted to determine which portion of the blood or tumor extracts contains the tumor-producing material. Studies of *spontaneous* avian sarcomata and leukoses indicated that the infectious material was present in both the blood cells and the cell-free material, namely, plasma, serum or extracts obtained by centrifugalization or ultrafiltration (5, 15, 26, 33). Sedimentation at high speed of ultrafiltrates of plasma from the blood of chickens with erythromyeloblasic leukemia disclosed ultramicroscopic particles countable by the electron microscope which are closely related to the infectivity of the plasma and also to the presence of an enzyme dephosphorylating adenosine trisulphate (9, 28, 39). Tyrode solution containing particles sedimented from chicken plasma ultrafiltrates by a centrifugal force of 14,000 times gravity exhibited greater tumor-producing activity than that of the entire original ultrafiltrate (6).

It has been shown that plasma from the blood of chickens bearing *induced* sarcomata or leukoses or cell-free extracts of the tumors fail to bring about the growth of tumors in normal chickens although the cellular portions of the blood and of the tumor extracts were highly infectious (33, 35). Injections of cell-free plasma and tumor extracts from mice and rats bearing lymphosarcoma, leukemia or lymphoid tumors fail to produce the disease in normal animals, although the cellular portions are infectious (16, 17, 32). A number of investigators (19, 12, 13, 16, 28) have emphasized the importance of recentrifugalization of samples of plasma and of serum to clear them entirely of cells or fragments of cells. On the other hand, it was found

that both the cellular and the cell-free fractions of the blood and of the tumors from rabbits with infectious myxoma contained a tumor-producing material potent for certain strains of rabbits (20, 22, 38).

Summary

A comparison of the behavior of the Lewis lymphoma #8 with that of other blood-borne neoplasms shows considerable similarity as is indicated by the following results: I. The neoplastic cells were present in the blood stream of the lymphoma-bearing rats implanted subcutaneously as early as 18 hours after implantation and persisted throughout the course of the disease. Transmission of lymphoma by means of whole blood was carried through twelve serial passages in rats of the Lewis inbred strain. Injections into susceptible rats of large amounts of blood from rats bearing induced sarcoma or fibrosarcoma failed to bring about the growth of tumors. II. The amount of blood required to bring about the growth of lymphoma was exceedingly small. It varied from 1 to 2 ml of a suspension formed by one drop of blood diluted in 200 ml of salt solution to the imperceptible amount present in plasma and serum after centrifugalization. III. Lymphoma tissue remained transplantable after exposure to temperature of —17°C. for 24 or more days. Blood cells, however, failed to give rise to growth of a lymphoma in rats injected with blood after storage at temperatures of 4°C. or —17°C. for longer than six days. IV. The cellular fraction of the blood or tissue extracts gave rise to lymphomata. Injections of whole blood or of washed white blood cells from the blood of lymphoma-bearing rats produced lymphomata at the site of injection. Injections of twice recentrifugalized plasma, serum or saline washings of the buffy coat failed to transmit the disease.

Injections into inbred rats of large amounts of blood from rats of the same or alien strains failed to bring about the development of resistance to growth of subsequent implantations of native tumors in the treated rats.

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GROWTH IN BIZYGOMATIC FACE BREADTH DURING CHILDHOOD

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(Received for publication June 11, 1954)

This paper focuses attention on one item of facial growth studied directly on the living organism. It pertains to the first two decades of the human life cycle, to children residing in North America, and to research findings amassed between 1891 and 1954. Its purpose is twofold: to report a series of analyses on original data at annual ages between 4 years and 10 years, and to systematize prior investigations extending downward into the prenatal period and upward through adolescence.

The particular item is that measurement of upper face breadth known technically as bizygomatic diameter. In defining bizygomatic diameter on the living child, different workers have varied their choice of language. It was defined by Porter (1) as the greatest breadth between the narrow, bony ridges felt in front of the ears; by Gray and Ayres (2) as the breadth between the outermost parts of the zygomatic processes, with pressure as much as can be comfortably borne; and by Hrdlicka (3) as the distance between the most widely separated points on the external surfaces of the zygomatic arches, applying the tips of spreading calipers with sufficient pressure to feel resistance of the bone. The 1906 international agreement on cephalometry (3) warned that the dimension "should be searched for with care, for it is often located more posteriorly than one would expect." Herskovits (4) gave the additional caution to avoid sliding the tips of the calipers along the cheek bones in a way that gathers flesh and forms a "bunch at the back."

Measurements of upper face breadth other than bizygomatic diameter are excluded. For instance, there has been no attempt to encompass studies of bimalar diameter (5, 6, 7), biauricular diameter (5), or dimensions taken from points lying between the bimalar and bizygomatic landmarks (8).

Only measurements of bizygomatic diameter taken directly on the external face are considered. Data obtained from skulls (9, 10) and roentgenograms (11) fall outside the scope of the present study.*

Objectives

Major aims or objectives of the paper are:

1. To report original materials on the distribution of bizygomatic diameter at successive annual ages from 4 years to 10 years.
2. To provide norms for bizygomatic diameter that are conveniently usable with children of any age between 4 years and 10 years.
3. To assemble and order the previously published research findings for bizygomatic diameter on North American infants, children, and adolescents.
4. To compare averages for bizygomatic diameter on groups of children representing different dental stages, orthodontic classes, secular periods, and racial backgrounds.
5. To present original findings from analyses of growth increments and individual growth patterns in bizygomatic diameter.
6. To colligate what is known on relationships between bizygomatic diameter and other somatic traits, *e.g.*, head breadth, dental arch breadth, stature.

Original Data

The Subjects.—Original data were gathered over the years 1937-54 on 289 Iowa City white children. There were 156 males and 133 females.

From the standpoint of ethnic background, all of the children were of northwest European ancestry. Most of them met Hrdlicka's criteria for "Old American stock" (12), *i.e.*, with few exceptions, their parents and grandparents (a) all resided in North America from birth, and (b) were descendants of immigrants from the British Isles, Germany, Scandinavia or the Netherlands.

Socioeconomic status was predominantly above average. Nearly 60 per cent of the fathers were professional men; almost all of those remaining were engaged in managerial, commercial or skilled trade occupations.

* There are a few special exceptions to this general delimitation, *i.e.*, at appropriate points the roentgenographic investigation by Woods (11) is drawn upon.

The children studied during the years 1937 through 1945 were enrolled in the State University of Iowa preschool laboratories and experimental elementary school. They were examined at the schools in a long-term research program sponsored by the Iowa Child Welfare Research Station. Those added after 1945 were enrolled in the Facial Growth Study, a long-term research program begun in 1946 under the joint sponsorship of the Iowa Child Welfare Research Station and the College of Dentistry. In neither program was the selection of subjects influenced by dental condition or orthodontic need.

The Materials.—All anthropometric examinations were made under the supervision of the writer, and the procedure was the same with both series of children. Briefly characterized, the anthropometric procedure was meticulous. The tips of spreading calipers were placed against the sides of the face at numerous points along the lateral surfaces of the zygomatic arches; the anthropometrist kept the instrument in a horizontal plane, applied firm pressure, and carefully sought the greatest bizygomatic breadth. Always separate measurements were taken by two anthropometrists. When these differed by 1.0 mm. or less, their mean was accepted as the final record. In instances of greater discrepancy, each anthropometrist made a second measurement and the mean of the 4 determinations constituted the final record. This high standard of precision in data collection was necessary for the study of growth increments and individual growth patterns. These problems are not meaningfully investigated unless the records employed closely approximate true morphologic values.

Most of the subjects were measured at more than one age. The data include measurements at consecutive annual ages from 4 years to 9 years on 93 subjects, and from 5 years to 10 years on 149 subjects. Sixty-nine subjects were measured beginning at age 4 years and continuing seriatim through to age 10 years.

Means for Bizygomatic Diameter

Original Findings.—Table 1 presents means for bizygomatic diameter at successive yearly intervals from 4 to 10 years of age. These means were derived from the records on Iowa City white children described above. In all instances the records were obtained within a week of the child's birthday. Interpreted in conjunction with figures from column 2 of Table 1, it follows that 92 males and 84 fe-

males were measured within one week of age 4 years, 145 males and 129 females within one week of age 5 years, and so forth.

Representative findings from column 3 of Table 1 are:

1. Mean bizygomatic diameter for males is 110.5 mm. at age 4 years, 7.3 mm. larger at age 7 years, and larger by an additional 6.0 mm. at age 10 years.

TABLE 1

Bizygomatic Diameter (mm.): Measures of Central Tendency and Variability for North American White Children of Northwest European Ancestry Studied 1937-54.

Age*	N	Mean	$S.E._m$	S.D	$S.E._{sd}$	V
			Males			
4	92	110.5	0.51	4.84	0.36	4.4
5	145	113.5	0.39	4.68	0.27	4.1
6	156	115.8	0.37	4.57	0.26	4.0
7	153	117.8	0.37	4.57	0.26	3.9
8	140	119.8	0.39	4.59	0.27	3.8
9	117	121.8	0.45	4.86	0.32	3.9
10	92	123.8	0.50	4.76	0.35	3.9
			Females			
4	84	107.9	0.47	4.27	0.33	4.0
5	129	110.3	0.36	4.04	0.25	3.7
6	133	112.3	0.36	4.18	0.26	3.7
7	127	114.3	0.37	4.11	0.26	3.6
8	119	116.1	0.37	3.99	0.26	3.4
9	108	118.0	0.40	4.15	0.28	3.5
10	92	119.9	0.45	4.26	0.31	3.6

* Proceeding from left to right, the successive columns represent (1) age in years, (2) number of subjects, (3) arithmetic mean, (4) standard error of mean, (5) standard deviation, (6) standard error of standard deviation, and (7) coefficient of variation.

2. The means for females are consistently smaller than those for males. At no age is the difference less than 2.5 mm.

3. With advancing age, the sexes differ by slightly increasing amounts; their means are less than 3.0 mm. apart at age 4 years and practically 4.0 mm. apart at age 10 years.

Comparative Materials.—Means for bizygomatic diameter from previous investigations on North American children are displayed in Tables 2 to 4. Table 2 lists values reported at 6 selected ages between birth and 3 years, while in Tables 3 and 4 values are itemized for each successive biennial age from 4 to 18 years. Measures of central tendency based on les than 10 subjects were not accepted for reproduction.

TABLE 2

Bizygomatic Diameter (mm.): Means from 31 Samples of North American Children Studied at Selected Ages Between Birth and 3 Years.

Birth			6 Months			2 years			3 years		
Study	N	Mean	Study	N	Mean	Study	N	Mean	Study	N	Mean
					Males						
13[a]	163	77.5[c]	15	34	98.0[g]	2	21	111.5[i]	2	28	112.1[i]
14	818	73.0[e]				4	17	106.6[k]	17	17[p]	111.2
						15	39	106.0[i]	15	57	110.0[i]
2 months			1 year			16	162	105.0[n]	4	27	110.0[k]
15	51	88.6[g]	2	18	105.2[i]				18	50	107.3[r]
			15	19	101.2[g]				16	158	107.0[n]
					Females						
Birth			6 months			2	21	105.8[i]	2	23	107.9[i]
13	149	76.0[c]	15	44	94.7[g]	17	11[p]	105.5	17	15[p]	107.6
14	835	72.4[e]				4	11	104.8[k]	4	27	107.1[k]
						15	39	104.0[i]	15	49	107.0[i]
2 months			1 year			16	156	103.5[n]	16	149	105.0[n]
15	39	85.6[g]	15	20	100.2[g]						

[a] Each study is identified by its number in the list of references.
[c] About two-thirds of subjects white, one-third American Negro.
[e] White infants from "moderate income" to "very poor" economic groups.
[g] New York orphanage infants of many ethnic groups, "including Negroes."
[i] White children of above-average socioeconomic status.
[k] American Negro children.
[n] "Middle class, American-born, white children."
[p] The records on these children are incorporated in Study 2.
[r] Jewish children of "lower middle" class.

The tables carry means for North American white children at birth (14), 1 year (2), and every age thereafter (2, 15, 16, 18, 20, 22, 27; for North American Negro children at all ages from 2 years to 18 years (4); for North American children of Mexican ancestry at all ages from 4 to 18 years (19, 25); and for North American Indian children at ages 8 to 16 years, inclusive (23). Means representing different socioeconomic levels are tabled for white private school children (2, 27); for middle class, white children (16); for Jewish children of poor economic status (18, 20); and for children low on the economic scale, of Italian (20, 21), Central European (20) and Finnish lineage (21). The earliest studies pertain to the school ages (1, 22); their publication preceded the present report by 60 years.

Attention is called to the exceptionally low means from the investigation on intellectually superior children at ages 8 to 14 years (24). It is apparent that there is a systematic error in these values; its source, however, is unknown. The investigator defined the measurement as "greatest bizygomatic distance."

TABLE 3

Bizygomatic Diameter (mm.): Means from 94 Samples of North American Children Studied at Biennial Ages from 4 to 10 Years.

4 years			6 years			8 years			10 years		
Study	N	Mean	Study	N	Mean	Study	N	Mean	Study	N	Mean
					Males						
15	31	112.0[a]	18	50	118.4[a]	23	14	124.9[v]	23	19	129.3[v]
2	34	111.7[a]	20	63	117.3[a]	18	50	123.5[a]	18	50	127.7[a]
17	17[c]	111.7	1	608	117.2[p]	2	147	120.7[a]	2	173	124.7[a]
18	50	111.6[a]	21	52	117.0[r]	20	67	120.5[n]	15	31	123.0[a]
19	13	111.2[g]	20	45	116.3[a]	20	63	119.2[a]	20	106	122.7[n]
4	42	110.9[i]	2	114	116.3[a]	21	92	119.0[r]	20	210	122.6[a]
16	157	109.5[k]	21	40	116.0[t]	17	16[c]	118.9	21	92	122.0[r]
			17	20[c]	115.4	1	2062	118.8[p]	19	26	121.6[g]
			4	96	115.2[i]	19	19	118.2[g]	1	1922	121.6[p]
			15	22	115.0[a]	15	14	118.0[a]	25	103	121.6[g]
			19	23	114.7[g]	21	51	118.0[t]	4	169	121.0[i]
			22	68	113.8[p]	4	177	117.8[i]	21	69	121.0[t]
			20	101	113.0[t]	20	66	116.1[t]	20	79	120.0[t]
			16	168	112.5[k]	22	130	115.6[p]	16	187	120.0[k]
						16	164	115.5[k]	22	139	118.9[p]
						24	14	107.0[x]	24	35	109.0[x]
					Females						
15	29	112.0[a]	20	66	115.8[n]	23	15	121.1[v]	23	13	125.6[v]
2	34	109.4[a]	2	74	115.2[a]	2	100	118.8[a]	2	110	122.3[a]
4	29	108.9[i]	1	608	115.2[p]	20	65	117.7[n]	20	61	121.4[n]
16	155	107.0[k]	15	32	114.0[a]	1	2065	117.6[p]	25	89	120.2[g]
			20	45	114.0[c]	20	51	117.4[c]	15	19	120.0[a]
			19	15	113.4[g]	17	15[c]	117.4	4	53	119.6[i]
			4	69	113.4[i]	15	16	117.0[a]	1	1829	119.5[p]
			17	26[c]	112.9	4	86	116.6[i]	20	48	119.4[c]
			20	80	112.2[t]	19	21	115.6[g]	19	22	118.5[g]
			22	77	111.9[p]	22	104	115.0[p]	20	61	118.0[t]
			16	167	110.5[k]	20	70	114.8[t]	22	140	117.2[p]
						16	167	113.5[k]	16	195	116.5[k]
						24	15	104.0[x]	24	42	109.0[x]

[a] White children of above-average socioeconomic status.
[c] The records on these children are included in Study 2.
[e] Jewish children of "lower" (20) or "lower middle" (18) class.
[g] Children of Mexican ancestry, low economic level.
[i] American Negro children.
[k] "Middle class, American-born, white children."
[n] Children of Central European descent, low economic level.
[p] White urban school children of the 1890's.
[r] Boys of Finnish lineage, low economic level.
[t] Children of Italian ancestry, poor economic status.
[v] Mission Indian children of Southern California.
[x] Intellectually superior children.

TABLE 4

Bizygomatic Diameter (mm.): Means from 109 Samples of North American Children Studied at Biennial Ages from 12 to 18 Years.

12 years			14 years			16 years			18 years		
Study	N	Mean	Study	N	Mean	Study	N	Mean	Study	N	Mean
					Males						
23	22	131.1[a]	23	14	138.6[a]	23	15	141.1[a]	18	50	140.1[c]
18	50	131.0[c]	18	50	134.3[c]	18	50	137.4[c]	27	25	138.6[e]
27	22	127.0[e]	28	...	133.7[e]	28	...	136.3[e]	19	28	137.5[g]
2	247	126.6[e]	2	373	130.4[e]	2	292	134.0[e]	20	20	137.4[i]
15	34	126.0[e]	16	112	130.0[n]	27	32	133.9[e]	2	129	136.6[e]
19	33	125.9[g]	27	48	129.3[e]	19	33	133.6[g]	4	42	135.4[r]
20	148	125.3[t]	26	...	128.5[v]	26	...	133.5[v]	20	33	134.1[c]
21	98	125.0[k]	20	359	128.5[c]	4	130	131.6[r]	22	43	133.0[t]
16	226	125.0[n]	21	93	128.0[k]	21	101	131.0[k]	20	44	132.9[p]
21	80	125.0[p]	20	112	128.0[t]	21	93	131.0[v]			
20	358	124.3[c]	21	90	128.0[p]	20	137	130.6[c]			
4	220	123.9[r]	15	23	128.0[e]	20	38	130.5[t]			
1	1525	123.8[t]	4	279	127.8[r]	1	193	130.3[t]			
20	142	123.8[p]	19	30	127.7[g]	22	144	129.9[t]			
25	101	123.3[g]	1	898	126.8[t]	20	39	128.0[v]			
26	...	122.9[v]	20	137	126.0[v]						
22	158	122.1[t]	22	166	125.5[t]						
24	63	111.8[x]	24	26	114.3[x]						
					Females						
23	17	131.1[a]	23	20	136.4[a]	23	10	134.4[a]	27	16	131.9[e]
2	126	126.1[e]	28	...	131.0[c]	20	40	131.6[i]	20	33	131.5[i]
27	18	125.4[e]	19	33	128.1[g]	28	...	131.6[c]	4	150	130.9[r]
20	52	124.4[i]	2	108	128.0[e]	4	86	130.4[r]	2	51	130.6[e]
20	50	123.6[c]	16	167	128.0[n]	2	86	129.9[e]	19	38	130.4[g]
25	95	123.2[g]	4	47	127.4[r]	27	16	129.7[e]	20	69	130.1[c]
4	57	123.0[r]	27	14	127.4[e]	1	409	129.5[t]	20	89	129.4[p]
19	31	122.6[g]	20	59	126.9[i]	19	34	129.4[g]	22	67	127.7[t]
1	1526	122.4[t]	20	40	126.4[c]	20	27	128.5[c]			
15	12	122.0[e]	20	48	126.3[p]	26	...	128.5[v]			
20	57	121.6[p]	1	997	125.7[t]	20	29	127.3[p]			
22	155	121.4[t]	26	...	125.5[v]	22	103	126.8[t]			
26	...	121.2[v]	22	72	123.1[t]						
16	226	119.0[n]	24	29	111.8[x]						
24	45	109.2[x]									

[a] Mission Indian children of Southern California.
[c] Jewish children of "lower" (20) or "lower middle" (18) class.
[e] White children of above-average socioeconomic status.
[g] Children of Mexican ancestry, low economic level.
[i] Children of Central European descent, low economic level.
[k] Boys of Finnish lineage, poor economic status.
[n] "Middle class, American-born, white children."
[p] Children of Italian ancestry, poor economic status.
[r] American Negro children.
[t] White urban school children of the 1890's.
[v] Feeble-minded children.
[x] Intellectually superior children.

Composite and Comparative Findings.—For North American white children, an effort was made to obtain a composite portrayal of average growth in bizygomatic diameter from fetal life through adolescense. Davenport (26), by studying an unspecified number of "Carnegie Embryological" white fetuses, secured an average bizygomatic breadth of 31.0 mm. at 20 weeks of gestation.* Comparison of this value with the mean bizygomatic diameter reported by Bakwin and Bakwin (14) on 1,653 newborn white infants, shows that during the last half of prenatal life upper face breadth increases over 40.0 mm. or, in relative terms, more than 130 per cent.

At successive biennial ages from 2 years to 18 years, composite means were computed on North American white children studied during the present century. Examination of Tables 2 to 4 shows that the number of studies available for combination varied with age and sex. Use was made of every appropriate age-sex sample from Table 1 and from Tables 2 to 4 (2, 15, 16, 18, 20, 21, 27). To illustrate: At 4 years of age there were 5 qualifying samples on boys (see Table 1 and Table 3 (15, 2, 18, 16). Their synthesis involved multiplying each mean by its N, summing the 5 products, summing the 5 N's, and dividing the first summation by the second. The result was a composite mean of 110.5 mm. on a combined sample of 364 white boys. Table 5 presents the entire series of composite values obtained. It will be seen:

1. Growth in upper face breadth during the first biennium of post-natal life is slow in relation to its growth during the fetal period and rapid in relation to its growth during the childhood years.

2. There is continual increase in average breadth of the upper face throughout childhood and adolescence. The increase is somewhat greater for the period 2 to 6 years than for any ensuing 4-year period.

3. At every age studied, the average North American white male has a broader upper face than the average female. Differences between the composite means are 2.0 mm. at 2 years, 3.4 mm. at 10 years, and 6.2 mm. at 18 years.**

* It is relevant to note that Scammon and Calkins (5), utilizing 369 Minnesota white fetuses at assorted ages, obtained a mean for bimalar diameter of 31.6 mm. at 20 weeks of gestation.

** At 18 years of age the average white female has an upper face breadth practically equivalent to that of early adulthood; Steggerda and others (29) obtained a mean of 130.5 mm. at 20 years of age on 100 Smith College women. The average increase between 18 and 20 years of age in males will be considered later.

TABLE 5

Bizygomatic Diameter (mm.): Composite Means at Successive Biennial Ages from Birth to 18 Years for North American White Children Studied During the Last Half Century.

Age in Years	Males		Females	
	N	Mean	N	Mean
Birth	818	73.0	835	72.4
2	222	105.8	216	103.8
4	364	110.5	302	108.0
6	811	115.2	597	112.7
8	854	118.9	588	116.0
10	1089	122.5	586	119.1
12	1405	125.3	541	122.2
14	1470	128.9	493	126.0
16	782	132.4	198	129.2
18	301	136.5	258	130.3

Findings from comparing selected series of means from Tables 2 to 4 with those of Table 5 are as follows:

1. The bizygomatic diameter of North American Negro children does not differ systematically from that of North American white children. Compared with the Herskovits (4) means at biennial ages from 2 to 18 years, corresponding means from Table 5 average 0.6 mm. higher for males and 0.8 mm. lower for females.

2. North American Mexican children 6 to 18 years of age show no consistent variation in bizygomatic diameter from North American white children. There is an average difference of less than 0.1 mm. between the means from Table 5 and the means for *mestizo* of low economic status from Goldstein (19) and Paschal and Sullivan (25).

3. The bizygomatic face breadth of North American Indian children is appreciably greater than that of North American white children. Boas' means (23) for Mission Indians 8 to 16 years of age are higher than the comparable means from Table 5 by an average of 7.3 mm.

4. On North American white children, there is evidence for the adolescent period of secular change in upper face breadth. Compared with the means based on 1909-54 data from Table 5, the means representing 1891-92 are lower from Porter (1) at ages 12 to 16 years by an average of 0.9 mm., and lower from West (22) at ages 12 to 18 years by an average of 2.6 mm.*

* A previous investigation by Boas (28) aligned means for bizygomatic diameter at

The composite means for males from Table 5 are presented graphically in Figure 1. In order to extend the curve to the end of the second decade of postnatal life, the mean bizygomatic diameter reported by Heath (30) on sophomore college men was utilized. This

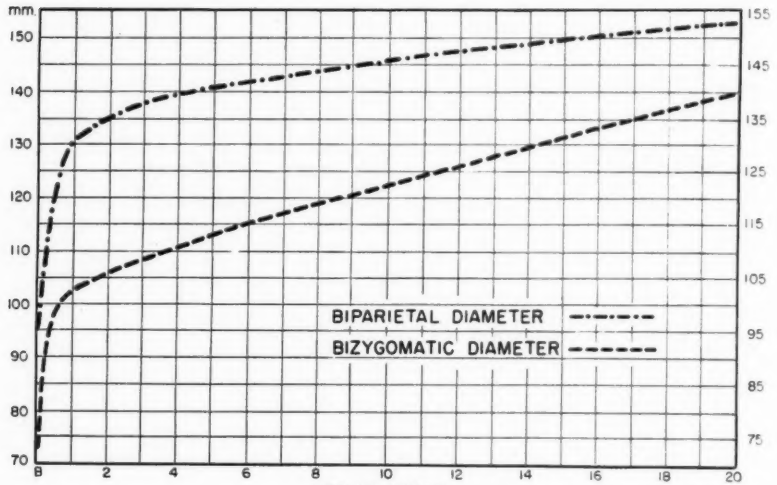

FIGURE 1

Growth curves for head breadth and upper face breadth over the period from birth to early adulthood. Each curve is drawn to composite means for North American white boys.

mean of 140.0 mm. was obtained from data collected at Harvard University over the years 1938-42 by Dr. Carl C. Seltzer. Figure 1 also includes a curve for biparietal diameter (head breadth) drawn to composite means for North American white males published in an earlier study (31).

With regard to the curve for head breadth, the earlier study stated that in North American white boys "approximately 60 per cent of size at age 20 is attained by birth, 80 per cent by 6 postnatal months, 90 per cent by 3 years, and 95 per cent by 9 years." Described in a similar manner, the curve for upper face breadth shows that in

ages 12.5 to 17.5 years from 1909 and 1936 samples of Jewish children residing in New York: the means for 1936 surpassed those for 1909 by an average of 0.5 mm. It is relevant, too, that at age 10 years the means from the present study (Table 1) exceed Porter's means by 1.3 mm. and West's means by 3.8 mm.

North American white boys less than 55 per cent of size at age 20 is attained by birth, approximately 80 per cent by 4.5 years, 90 per cent by 12.5 years, and 95 per cent by 16 years.

Turning attention to postnatal *increase* in mean size, Figure 1 shows:

1. For biparietal diameter, 50 per cent of the amount gained in the first 20 years following birth is added during the first 7 months. For bizygomatic diameter, a period of about 2.5 years is taken to achieve the same percentage of postnatal gain.

2. Seventy-five per cent of the increment in mean biparietal diameter over the first score of postnatal years is registered by 3 years of age. A like percentage of the postnatal increase for mean bizygomatic diameter is not attained until after 10 years of age.

Before terminating this section, it is pertinent to attach an estimate of the difference between bizygomatic diameter taken over the soft tissues and on the skeleton. Use will be made of a longitudinal, roentgenographic study by Woods (11) on 14 children of each sex. From frontal roentgenograms corrected for distortion with a Wylie compensator, Woods obtained means which average 6.4 mm. less than the means of Table 5 and 7.0 mm. less than those of Table 1.

Variability in Bizygomatic Diameter

Absolute Variability.—Column 5 of Table 1 gives the standard deviations obtained on the previously described Iowa City white children at annual ages from 4 years to 10 years. It will be seen that at every age absolute variability in bizygomatic diameter is less among females than among males. Explicitly, the standard deviations for females vary between 4.0 mm. and 4.3 mm., those for males between 4.6 mm. and 4.9 mm.

Throughout the first 20 years of postnatal life, there is practically no change in the absolute variability of bizygomatic diameter. Standard deviations at birth are available from Bakwin and Bakwin (14) and from Freeman and Platt (13). The latter reports 4.5 mm. on 163 males; the former, 4.9 on 818 males. For females, the N's were 149 and 835 respectively, and the standard deviations 3.9 mm. in each instance. In the second decade, standard deviations of 4.9 mm. have been reported on male samples of 247 subjects (2) representing age 12 years, 292 subjects (2) representing age 16 years, and 258 subjects (30) representing age 20 years. Parallel female sam-

ples of 126 (2), 86 (2) and 100 (29) gave standard deviations of 4.4 mm., 4.0 mm. and 4.2 mm.

Relative Variability.—As in the case of absolute variability, at all ages relative variability (V) is slightly greater for males than for females. In contrast, however, there is an overall decline with age in relative variability. This follows since the numerators used in calculating the coefficients of variation (the standard deviations) remain essentially constant, while the denominators (the means) increase with age.

For males, the coefficients of variation decrease from roughly 6.0 per cent at birth (13, 14), through 4.0 per cent at 6 years of age (see Table 1), to 3.5 per cent at 20 years of age (30). For females, the decline is from approximately 5.3 per cent at birth (13, 14), through 3.7 per cent at 6 years (Table 1), to 3.2 per cent at 20 years (29).

Norms Based on Percentiles.—Readily usable norms for upper face breadth are presented in Figure 2. On each sex 5 descriptive zones have been graphed; they are designated Broad Upper Face, Moderately Broad, Average, Moderately Narrow, and Narrow Upper Face.

Figure 2 was derived from the original records for bizygomatic diameter obtained on Iowa City white children. Consequently, it extends over the age period from 4 years to 10 years and depicts the same distributions as are tabularly described in Table 1.

The basic statistics obtained from each distribution for the construction of Figure 2 were: the minimum value; the 10th, 30th, 70th, and 90th percentiles; and the maximum value. These statistics served to section the distributions into 5 adjoining segments. The minimum and 10th percentile constituted the boundary values of the first segment, the 10th and 30th percentiles the boundary values of the second segment, and so forth.

Graphic construction of the two "frames of reference" can be indicated sufficiently by tracing development of the "Average" zone for one sex. The 30th percentiles for boys at consecutive annual ages from 4 years to 10 years were plotted against age, and a line was drawn connecting the succession of points. This established the lower boundary of the zone. Similarly, by plotting and graduating the 70th percentiles for boys the upper boundary of the zone was determined.

It remains to illustrate use of the norms. Assume that measurements of 114 mm. and 111 mm. have been obtained on 2 white boys aged 5 years and 8 years, respectively. Reference to Figure 2 shows

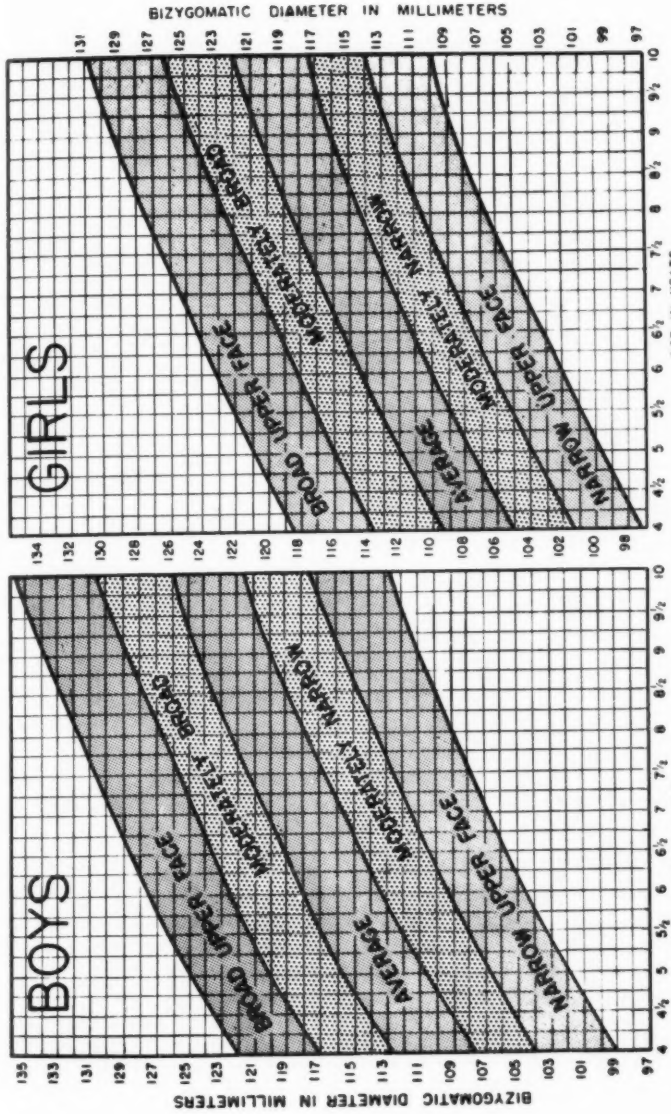

FIGURE 2

Norms for bizygomatic diameter derived from 1937-54 data on North American white children.

that upper face breadth is "Average" in the one instance, and "Narrow" in the other. Again, assume that measurements of 117 mm. and 115 mm. are secured for 2 girls aged 6 years and 9.5 years. On referring their records to Figure 2, one girl is found to have a "Moderately Broad" upper face, and the other a "Moderately Narrow" upper face.

Bizygomatic Diameter on Odontic Groups

Dental Stages.—Hellman (32) and Krogman (33) have grouped measurements of upper face breadth according to the dental stage, rather than by age. Results from their analyses are reproduced in Table 6.

TABLE 6

Bizygomatic Diameter (mm.): Measures of Central Tendency and Variability on Children Classified According to Hellman's Dental-stage Scale.

Dental Statge	Males N	Mean	S.D.	Females N	Mean	S.D.
		HELLMAN, 1925-30 DATA				
II A	17	117.1	6.0	19	113.3	5.0
II C	13	119.8	5.6	15	116.8	4.1
III A	114	121.3	5.1	107	119.3	4.9
III B	122	123.4	4.8	158	123.2	5.5
III C	56	126.5	5.1	68	125.4	4.6
IV A	154	130.4	6.1	252	128.1	4.7
IV C	21	137.2	4.7	22	132.0	4.3
		KROGMAN, 1948-50 DATA				
III A	42	122.0	5.7	45	113.1	5.9
III B	131	122.4	5.6	157	119.2	4.8
III C	19	125.6	4.5	25	123.6	5.2
IV A	31	128.6	4.7	42	125.0	5.5

Succinctly, inclusion in the progressive dental categories was determined by: II A, eruption of the deciduous second molars; II C, eruption of one or more permanent first molars; III A, eruption of permanent first molars and one or more permanent incisors; III B, exfoliation of one or more deciduous molars and eruption of successor; III C, eruption of one or more permanent second molars; and IV A, eruption of all permanent second molars; and IV C, eruption of one or more permanent third molars.

Hellman's subjects were "all of white extraction and born in the United States, most of them in New York City." Although seen in private orthodontic practice, they encompassed "all sorts of occlu-

sion." Krogman characterized his subjects as "a typical cross section of a grade school population in Philadelphia."

Occlusal Classes.—Hellman (34) and Goldstein and Stanton (35) have reported findings for bizygomatic diameter from subgrouping according to both dental stage and occlusal class. The former studied girls only, and the latter boys only. Both studies were made in New York; Hellman's on orthodontic patients, Goldstein and Stanton's on Jewish boys of the lower middle class.

The upper portion of Table 7 presents Hellman's results from sub-

TABLE 7

Bizygomatic Diameter (mm.): Measures of Central Tendency and Variability on Children Subgrouped by Dental Stage and Occlusal Class.

Hellman Dental Stage	Class I			Class II, Div. 1			Class II, Div. 2		
	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.
Angle Occlusion Category: Females									
III A	51	119.2	4.9	26	119.7	5.1	26	119.9	4.8
III B	86	123.5	5.2	28	123.5	6.7	31	122.9	4.2
III C	23	125.7	3.4	18	124.0	5.3	22	125.9	4.0
IV A	128	128.6	4.2	87	128.5	5.2	20	127.6	3.4

	Stanton Occlusion Category: Males					
	Normal			Abnormal		
	N	Mean	S.D.	N	Mean	S.D.
II A	37	114.5	6.7	58	109.8	5.5
III A	22	124.4	5.8	104	125.2	5.0
IV A	44	137.1	4.7	116	136.3	5.6

grouping by dental stage and Angle class. The lower portion of the table reproduces Goldstein and Stanton's results from subgrouping according to the Hellman dental stages and ratings of occlusion as normal or abnormal. It will be observed that the table yields no evidence of a relationship between bizygomatic diameter and dental occlusion.

The Bizygomatic Diameter of Individuals

As stated earlier, the original data on Iowa City white children included annual measurements for 69 individuals extending uninterruptedly from 4 to 10 years of age. The records for 8 of these individuals were selected for presentation. Selections were made with the objective of portraying the extremes of normal variation for growth in bizygomatic diameter over the period from 4 to 10 years.

TABLE 8

Bizygomatic Diameter (mm.): Annual Records on 8 Children Illustrating Normal Variation in Growth Over the Period from 4 to 10 Years of Age.

Sex	Age in years: 4	5	6	7	8	9	10	Millimeter Increment
	Individuals increasing more than 13 per cent							
Male	109.5	113.0	116.0	118.0	121.0	125.0	128.0	18.5
Male	117.5	121.0	124.5	128.0	131.5	133.5	135.0	17.5
Female	107.5	110.0	113.0	116.0	118.5	120.5	122.5	15.0
Female	105.0	108.0	111.0	113.5	115.5	118.0	119.0	14.0
	Individuals increasing less than 9 per cent							
Male	109.0	112.0	114.0	115.0	116.0	117.0	118.0	9.0
Male	112.0	113.0	114.0	115.0	116.5	118.0	120.0	8.0
Female	109.0	111.5	112.5	113.5	114.5	116.0	117.0	8.0
Female	108.5	109.5	111.0	113.0	114.0	115.0	116.0	7.5

Table 8 gives the records for 2 individuals of each sex showing rapid growth, and 2 individuals of each sex showing slow growth. Over the 6-year period, the rapidly growing individuals made absolute gains of not less than 14.0 mm., and relative gains of not less than 13 per cent. The slowly growing individuals gained no more than 9.0 mm., or 9 per cent. Figure 3 depicts graphically the growth curves for 4 of the 8 individuals.

Measurements of bizygomatic diameter on 3 normal children, 2 boys and a girl, were published by Gray (36). For the girl, there were 13 records extending from 117 mm. at 4.6 years, through 122 mm. at 6.0 years and 133 mm. at 13.2 years, to 135 mm. at 17.0 years. For the boys, the records covered shorter periods; on the one from 134 mm. at 9.0 years, through 142 mm. at 13.2 years, to 149 mm. at 20.1 years and, on the other, from 134 mm. at 10.0 years, through 144 mm. at 15.0 years, to 148 mm. at 20.9 years.

Records for bizygomatic diameter were reported by Brintle (37) on a set of female quadruplets of "Old American stock", born and reared at Hollis, Oklahoma. The children were measured at 12.5 years of age by Dr. Leslie Spier. It was considered "probable that . . . the four individuals developed from three eggs." The 4 records were 111 mm., 112 mm., 113 mm., and 114 mm.

Davenport (26) graphed the growth of individuals in bizygomatic diameter over varying segments of the period from 5 to 20 years of age. His graphs represented (a) 13 feeble-minded boys, (b) 3 orphanage girls, (c) 18 members of three family groups, (d) 3 pairs

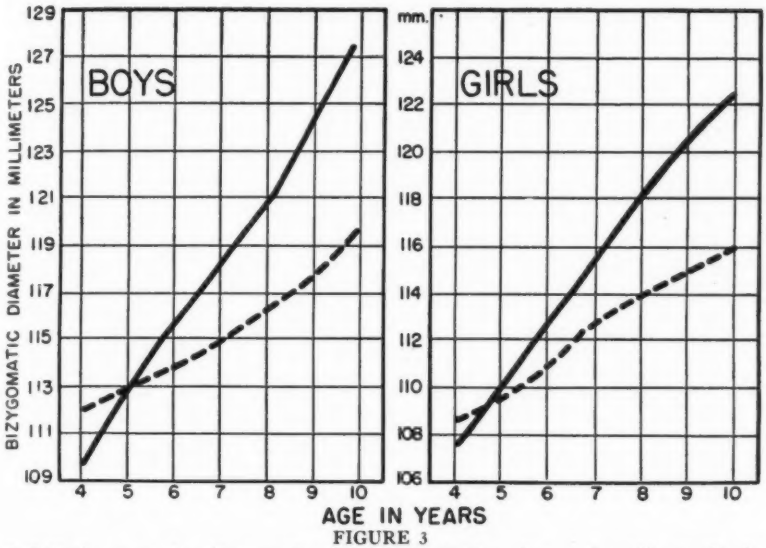

FIGURE 3

Individual curves for bizygomatic diameter illustrating slow and rapid growth in children of both sexes.

of monozygotic twins, (e) a pair of dizygotic twins, and (f) 5 physically pathologic children. For the physically pathologic individuals, approximate values read from the graphs were 122 mm. at 8 years and 133 mm. at 18 years on two female cretins, 130 mm. at 16 years on a female achondroplastic dwarf, 108 mm. at 14 years and 117 mm. at 18 years on a female ateliotic dwarf, 104 mm. at 12 years and 117 mm. at 18 years on a male microcephalic youth. The plotted records for one pair of monozygotic twins age 8 years were roughly 112 mm. and 113 mm.; for the other one-egg twins, readings at age 16 years were 124 mm. and 125 mm. on one pair, 129 mm. and 130 mm. on the other.

Information on chronologic age, sex, dental stage, occlusal classification, and bizygomatic diameter was presented for 8 individuals by Krogman (38). The youngest individual was 8.3 years of age (female, Hellman stage III A, normal occlusion, 123 mm.) and the oldest individual 16.9 years (female, Hellman stage IV A, Angle class III, 124 mm.). The largest upper face breadth was 131 mm. (male, 11.7 years of age, Hellman stage III B, Angle class I) and the smallest

117 mm. (female, 10.1 years of age, Hellman stage III B, Angle class I).

Increment Analyses for Bizygomatic Diameter

Freeman and Platt (13) analyzed gains in bizygomatic diameter derived from measurement of 71 infants at birth and 30 days later. Separated by sex, these gains over the first postnatal month gave means of 7.2 mm. on the 31 males and 7.1 mm. on the 40 females.

Increments derived from the original data of the present study were distributed for each successive annual period and for 2 quinquennial periods. The results are presented in Tables 9 and 10. Table 9 shows:

TABLE 9

Bizygomatic Diameter (mm.): Analysis of Increment Values Representing the Growth of North American White Children During 6 Annual Intervals Between 4 and 10 Years of Age.

Interval (Years)	N	Percentage showing millimeter gain of: 1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0	Mean Increase
Males											
4-5	80	1	5	18	20	26	20	6	3	1	2.8
5-6	139	3	12	37	25	17	4	2			2.3
6-7	144	7	21	37	24	8	2	1			2.1
7-8	140	9	26	36	17	9	2	1			2.0
8-9	121	10	27	36	19	5	2	1			2.0
9-10	96	11	28	41	15	4	1				1.9
Females											
4-5	64	5	22	28	20	14	6	5			2.3
5-6	100	7	30	31	17	11	4				2.0
6-7	103	5	29	42	18	4	2				2.0
7-8	109	10	26	39	18	7					1.9
8-9	106	11	22	50	15	2					1.9
9-10	92	15	30	42	12						1.8

1. Between 4 and 5 years of age, individuals varied in amount of gain in bizygomatic diameter from 1.0 mm. to 5.0 mm. in the case of boys and from 1.0 mm. to 4.0 mm. in the case of girls. Eighty-four per cent of the boys gained between 2.0 mm. and 3.5 mm., 84 per cent of the girls between 1.5 mm. and 3.0 mm.

2. During the tenth year of postnatal life, variations in increase among males spread between 1.0 mm. and 3.5 mm., with 69 per cent of the group clustered at 1.5 mm. and 2.0 mm. Corresponding extreme limits for females are 1.0 mm. and 2.5 mm., with 72 per cent of the group at 1.5 mm. or 2.0 mm.

3. The increment means are slightly higher on males than females at each year studied, and they decrease with age in both sexes.

TABLE 10

Bizygomatic Diameter (mm.): Analysis of Increment Values Representing the Growth of North American White Children During 2 Quinquennial Periods Between 4 to 10 years of Age.

Interval (Years)	N	Percentage showing millimeter gain of: 5.0 to 6.5	7.0 to 8.5	9.0 to 10.5	11.0 to 12.5	13.0 to 14.5	15.0 to 16.5	Mean Increase
				Males				
4-9	42	2	12	36	33	10	7	11.0
5-10	74	3	24	39	22	9	3	10.2
				Females				
4-9	51	4	18	47	21	10		10.0
5-10	75	5	26	47	21	1		9.5

Findings from Table 10 are:

1. Between 4 and 9 years of age, the mean increment in bizygomatic diameter is 11.0 mm. on the sample of boys, and 1.0 mm. less on the sample of girls. In each instance the mean is approximately equivalent to the sum of the Table 9 means for 4-5 years through 8-9 years.

2. For both quinquennia, the amounts of individual gain in bizygomatic diameter are more variable among males than among females. To illustrate: Gains between 9.0 mm. and 10.5 mm. are found for nearly 50 per cent of the females and for less than 40 per cent of the males.

It is fitting in this section to include increment materials from Woods' study (11). These data were obtained from serial frontal roentgenograms corrected for distortion. The sample included a like number of boys and girls, but the numbers were too small for division by sex. Table 11 displays the findings on 22 individuals for the decennium 3 to 13 years, and on 24 individuals for the decennium 5 to 15 years. The gains for the former ranged from 14.0 mm. to 23.0 mm., those for the latter from 11.5 mm. to 22.5 mm.

Twenty-one of Woods' subjects had serial records extending from 3 years to 15 years. The individual gains for this 12-year span were scattered between 17.5 mm. and 27.5 mm., and gave a mean of 22.7 mm.

TABLE 11

Bizygomatic Diameter (mm.): Analysis of Increment Values for 2 Decennial Periods. From Roentgenographic Data Obtained by Woods on a Small Group of North American Children of Both Sexes.

Interval (Years)	N	Percentage showing millimeter gain of: 11.5 to 13.0	13.5 to 15.0	15.5 to 17.0	17.5 to 19.0	19.5 to 21.0	21.5 to 23.0	Mean Increase
3-13	22		5	18	27	27	23	19.3
5-15	24	8	13	29	33	13	4	17.0

Correlations Involving Bizygomatic Diameter

Intrinsic Relationships.—Using the original data on Iowa City white children, the association was studied between bizygomatic diameter at age 4 years and bizygomatic diameter at age 9 years. Pearson product-moment correlation coefficients of 0.89 were obtained on each sex. The N's were 42 and 51 for males and females respectively. Similarly, coefficients of correlation were calculated from the data for bizygomatic diameter on the 74 males and 75 females measured at ages 5 to 10 years. Here, the *r*'s were 0.90 in each instance.

Two facets of the association between size and gain were investigated: (a) bizygomatic diameter at age 4 years was correlated with increase in bizygomatic diameter between 4 and 9 years, and (b) bizygomatic diameter at age 10 years was correlated with increase in bizygomatic diameter between 5 and 10 years. The coefficients obtained for size at age 4 with gain during the ensuing quinquennium were —0.29 for the 42 males and —0.21 for the 51 females. In the case of size at age 10 and gain during the antecedent quinquennium, the obtained *r*'s were 0.40 on the 74 males and 0.36 on the 75 females. These results are statistically significant and reciprocal; they allow the generalization that a slight relation exists between size and gain during middle childhood.

Extrinsic Relationships.—An earlier report on Iowa City white children (39) included findings at ages 5 and 7 years on the relation of bizygomatic diameter to dental arch breadth. The arch measurement was "maximum horizontal distance between the buccal surfaces of the maxillary deciduous second molars." For both ages and sexes the obtained coefficients were similar. Specifically, the *r*'s were 0.31

on 36 boys aged 5 years, 0.33 on 34 girls aged 5 years, 0.36 and 0.32 on 28 children of each sex aged 7 years.*

Correlation coefficients at ages 4 and 10 years were computed from the original data of the present study for bizygomatic diameter with head breadth (biparietal diameter), and bizygomatic diameter with stature (soles-vertex distance). Again, the N's were 42 and 51 at 4 years, 74 and 75 at 10 years. For bizygomatic diameter with biparietal diameter the obtained *r*'s were 0.60 and 0.68 on boys and girls aged 4 years, 0.64 and 0.65 on boys and girls aged 10 years.** Listed in the same order the *r*'s for bizygomatic diameter with stature were 0.24, 0.31, 0.45, and 0.28.

For information bearing on the relation of bizygomatic diameter to birth order, growth of the pubic hair and breadth of the anterior teeth, the reader is referred to articles by Bakwin and Bakwin (14), Boas (20), and Sears (43). The Bakwin and Bakwin article pertains to the neonatal period, the Boas article to the adolescent years, and the Sears article to adulthood. Sears posits: "The combined widths of the upper incisors and cuspids in pleasing natural dentures will be found to measure slightly less than one-third of the greatest facial width at the cheek bones."

Summary

The topic treated is the growth of North American children in breadth of the upper face, *i.e.*, bizygomatic diameter. A dual research task is performed: the procedures and results of an original investigation are described, and the total existing knowledge on the topic is synthesized.

The original data were accumulated between 1937 and 1954 in a longitudinal study of white children made at Iowa City, Iowa. These data, collected at annual intervals between 4 and 10 years of age, were subjected to several types of statistical and graphic analysis.

In obtaining the synthesis of present knowledge, investigations ex-

* On a sample of 111 "white American" adult males, Channing and Wissler (40) secured a Pearson *r* of 0.38 for bizygomatic diameter with minimum distance between the lingual surfaces of the maxillary first molars "at the gum line." Bakwin and Bakwin (41), on 100 white newborn males obtained *r*'s of 0.50 and 0.40 from correlating bimalar face breadth with maximum breadth and length of the palate.

** Boas (42), on a sample of 239 Sioux Indian adult males 20 to 59 years of age, reported *r*'s of 0.52 for head breadth with upper face breadth, and of 0.27 for head length with upper face breadth.

tending back to 1891 were drawn upon. The age period covered began with early fetal life and continued to young adulthood.

Problems given consideration include: mean bizygomatic diameter at successive ages; racial, secular and sex differences in bizygomatic diameter; absolute and relative variability in bizygomatic diameter; bizygomatic diameter on children typifying different dental stages and orthodontic classes; increases in bizygomatic diameter over annual, quinquennial and decennial periods; individual growth curves for bizygomatic diameter; the association between bizygomatic size and gain; and the relation of bizygomatic diameter to other somatic traits.

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BOOK REVIEW

Dynamics of Growth Processes. (Eleventh Symposium of the Society for the Study of Development and Growth, held at Williams College, Williamstown, Mass., in June, 1952). Edited by E. J. Boell. Princeton University Press, 1952. $7.50.

A few years ago when I was a graduate student a number of other students and myself were urged to join the Society for the Study of Development and Growth. It was not that there was a completely desperate need for members, but the group was a bit on the small side, and a little genteel campaigning was in order. By now the Society is well known and the membership list has long reached the limit; in fact, there is almost a waiting list of hopefuls watching for some of us veterans to die or to fail to send in our annual dues.

Part of the reason for this increase in popularity of the Society is, I suppose, because the number of people interested in development and growth has increased with the rest of the population. The other reason is that the symposia published until this year by this Journal, have become well known. They deserve their good name because each year they have contained some stimulating articles by stimulating scientists and this year's symposium is no exception.

There has been a change in the tradition and for the first time the Symposum has been published as a book. In this case a particularly well printed and well illustrated book has been turned out by the Princeton University Press which will continue to do the series in the future.

A number of these papers are on old themes that have appeared repeatedly in the past symposia. This does not mean that what is said in the paper is not new and interesting or well put and as a perfect example to illustrate my point, G. Fankhauser's article on the nucleus and cytoplasm is an exemplary piece of exposition. Other papers dealing with familiar problems are F. W. Went's discussion of the physical factors affecting plant growth, F. Skoog's and R. Gaunt's respective discussion of the chemical control of growth in plants and animals, D. A. Sholl's discussion of problems connected with growth curves, G. E. Dickerson's review of size inheritance in animals, and F. E. Smith's paper on population growth.

The majority of the remaining papers are on subjects that almost

did not exist ten years ago when the Society was getting under way. L. M. Kozloff, for instance, discusses the mechanism of synthesis of phage as revealed primarily by the use of radioactive isotopes, and K. R. Porter examines the cell with the latest and most improved methods of the electron microscope, and A. W. Pollister brings together what we know of the sites of protein synthesis within the cell. A. Novick and L. Szilard also have something quite new with their chemostat, with which they can study the kinetics of synthetic processes. All these subjects and usually the methods were either unknown or unexploited a few years back. I am not sure that because they are new they are telling us more about growth and development than the old way, but the two together (as they are in this volume), give an impressive battery of approaches.

The reader should be warned that it is absolutely impossible to read this book from cover to cover in one or two sittings. Some of it is well written and some quite badly written; some of it is clear and some is difficult, but if one reads it as a journal, skimming in some places and bearing down in others, there are both enjoyments and rewards waiting for you.

JOHN TYLER BONNER